



An Overview of Neuroendocrine Tumour Markers

Nöroendokrin Tümör Belirteçlerine Genel Bir Bakış

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Abstract

As there are many different subtypes of neuroendocrine tumors (NETs), many kinds of markers are used for their diagnosis and follow-up. Most of these markers, such as calcitonin, catecholamines, 5-hydroxyindoleacetic acid (5-HIAA), insulin, gastrin, pancreatic polypeptide, and glucagon are specific to one subtype of NET. In addition, there are also general markers used in various NET subtypes; the most commonly used ones are chromogranin-A (CgA), neuron-specific enolase (NSE), and synaptophysin. The sensitivity and specificity levels of CgA are highest among all NET markers. However, specific markers, such as calcitonin in medullary thyroid carcinoma, insulin in insulinoma and catecholamines in feochromocytoma are more useful than CgA. CgA is an auxiliary marker in cases with relapse or metastasis of such functional NETs. Carcinoid syndrome is characterized by serotonin hypersecretion with the other products and 5-HIAA level is used to determine the serotonin hypersecretion. Thus, 5-HIAA is the specific marker for carcinoid tumors which comprise two-thirds of all NETs. *Türk Jem 2014; 18: 132-136*

Key words: Neuroendocrine tumors, tumor markers, chromogranin A, neuron-specific enolase, 5-hydroxyindoleacetic acid

Özet

Pek çok farklı alt tipleri bulunduğundan, nöroendokrin tümörlerin (NET) tanı ve takibinde birçok belirteç kullanılmaktadır. Kalsitonin, katekolaminler, 5-hidroksi indol asetik asit (5-HIAA), insülin, gastrin, pankreatik polipeptid ve glukagon gibi belirteçlerin çoğu NET'in tek bir alt tipine spesifiktir. Bununla birlikte, çoğu NET alt tipinde birlikte kullanılan genel belirteçler de mevcuttur. Bunlardan en yaygın şekilde kullanılanlar Kromogranin-A (CgA), nörona spesifik enolazdır ve sinaptofizindir. NET'lerin hepsi birlikte ele alınınca en duyarlı ve en spesifik olan belirteç CgA'dır. Ancak medüller tiroid kansinomunda kalsitonin, insülinomada insülin ve feokromositomada katekolaminler gibi spesifik belirteçler fonksiyonel NET'lerde CgA'dan daha yararlı olduğundan, bu tümörlerde CgA özellikle nüks veya metastaz yapmış olgularda yardımcı bir belirteç olarak kullanılmaktadır. Karsinoid sendrom diğer ürünlerle birlikte serotoninin aşırı sekresyonu ile karakterizedir ve serotoninin aşırı üretimini belirlemek için 5-HIAA ölçümü kullanılmaktadır. Dolayısıyla, 5-HIAA tüm NET'lerin üçte ikisini oluşturan karsinoid tümörlerin spesifik bir belirteçidir. *Türk Jem 2014; 18: 132-136*

Anahtar kelimeler: Nöroendokrin tümör, tümör belirteçleri, kromogranin-A, nöron-spesifik enolaz, 5-hidroksiindolasetik asit

Introduction

Neuroendocrine tumors (NETs) had been a little-known and very rare disease before the last two decades. However, recently, they have been recognized earlier and more frequently. Now, the annual incidence of NETs is estimated at about 2.5-5 per 100.000 people and the prevalence is 35 per 100.000 people (1).

The main reason for classifying different kinds of tumors in the same group, the NET group, is their common neurohormonal characteristics. Indeed, all neuroendocrine cells and NETs have similar neurohormonal granules which contain neuroamines and/or polypeptide hormones. Additionally, because neuroendocrine cells migrate in the embryonic life, NETs may occur in anywhere of the body, sometimes at an irrelevant site. They also have different embryonic origins, functional features and tumor behaviors (2,3,4). Although most NETs are slowly growing and silent for a long time, some of them are rapidly growing and metastatic tumors.

As a result, there are lots of NET subtypes, such as carcinoid tumors, pheochromocytomas, pancreatic neuroendocrine tumors, medullary thyroid carcinomas, small cell lung cancers, large cell lung cancers, pituitary adenomas, and neuroblastomas. NETs of the gastrointestinal tract and pancreas can together be called as GEP-NETs. Pancreatic NETs may be nonfunctioning or functioning and overproduce gastrin, glucagon, insulin, somatostatin, or vasoactive intestinal peptide (5,6). Importantly, about 65% of NETs are carcinoid tumors which occur more often in the gastrointestinal tract (90%), and rarely in the bronchus, thymus, or other organs. Most of the carcinoid tumors are detected in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%) within the gastrointestinal tract (7).

Herein after, we will focus on the most commonly used, therefore, the most important biochemical markers by reviewing the recent English medical literature. In addition, we will discuss some frequently encountered issues about NET markers.

Net Markers

As there are numerous subtypes of NETS, there are numerous kinds of NET markers (Table 1) (5,6,7,8). Most of the markers, such as 5-HIAA (5-hydroxyindoleacetic acid), insulin, gastrin and calcitonin can be considered to be specific to one subtype of NETs. It is noteworthy that, levels of a specific NET marker may also mildly increase in some other NETs, but not as much as the certain subtype. For example, serum calcitonin levels are generally higher than 100 pg/mL in medullary thyroid carcinoma while elevated levels between 20-100 pg/mL are frequent in other NETs, especially in metastatic NETs. On the other hand, chromogranins, synaptophysin, and neuron-specific enolase (NSE) should be considered general NET markers, because they are not specific to one NET subtype. High levels of general markers may be observed in either peripheral blood or immunohistochemical analysis of NETs.

Importantly, a high level of tissue positivity is independent from the secretory activity in most of NETs. This rule should be kept in mind for either general or specific markers. For example, a pheochromocytoma with no preoperative elevation in catecholamine levels can be detected in postoperative immunohistochemical analysis. Additionally, levels of either general or specific markers should be a part of the initial and follow-up evaluation of NETs but cannot be relied on as the sole workups. They have to be considered together with other clinical findings and studies, especially the imaging studies.

Neuron-Specific Enolase

Serum measurement of NSE is not very useful except for patients with small cell lung cancer and neuroblastoma, because, despite of its specificity (86%), its sensitivity is very low (36%) in NETs (9). In addition, specificity and sensitivity of NSE in carcinoid tumors is 100%, and 33%, respectively (10). As seen, the disadvantage of NSE is its low specificity. An advantage of NSE is that it is not associated with tumor secretory activity. Additionally, if serum level of NSE is found to be elevated, it should be evaluated as a bad prognostic factor in some NETs. For example, the presence of elevated levels of serum NSE in a patient with pheochromocytoma may predict malignant behavior of the tumor.

Chromogranins

Chromogranins, also called as secretogranins, are polypeptide prohormones which are the major constituents of dense-core secretory granules in NET tissues (11). The eight subtypes of chromogranins are: chromogranin A (CgA), chromogranin B (CgB), chromogranin C (CgC), secretogranin III (SgIII), SgIV, SgV (7B2), SgVI (NESP55), and nerve growth factor (VGF). Circulating CgC (also known as secretogranin II) levels are rarely elevated in NETs. Although the most frequently used one is CgA, CgB levels are also elevated in most of the NETs (12).

The function of CgA is not known clearly, but it seems that they have important roles in secretory granulogenesis and secretory protein sorting (11,12,13,14,15). Serum CgA levels generally correlate with number of dense-core granules in neuroendocrine

cells. It can be measured by either immuno-enzymatic (ELISA) or radio-immunometric (RIA) assays. The sensitivity and specificity of CgA is about 80-100% in either functional or non-functional NETs. Therefore, CgA can be considered the most sensitive and specific diagnostic marker when all NETs taken together (11,12,13,14,15). In addition, CgA can also be used in monitoring the results of NETs treatment. For example, a reduction of >50% in serum CgA levels reflects a positive response to the medical therapy in NETs (11). Additionally, CgA levels are lower in early stages of NETs compared to that in late stages and, CgA levels can be found to be raised in almost all metastatic NETs (13).

As a general marker, serum CgA level is increased in most of NET subtypes (Table 1). The sensitivity of CgA is associated with the subtype of NETS, for example, in gastrinomas 100%, in pheochromocytomas 89%, in carcinoid tumors 80-100%, in non-functioning pancreatic NETs 69%, and in medullary thyroid carcinomas 50% (10,16). Although CgA levels are rarely elevated in insulinomas, their diagnosis has been established in the early stages because of severe symptoms of hypoglycemia. In addition, serum CgA is generally within normal ranges in poorly differentiated NETs while serum NSE is elevated (5). On the other hand, increase of CgA is very important in the non-functional NETs, because other markers are usually within normal ranges (16). However, specific NET markers are more sensitive and specific than CgA in functional NETs. For example, calcitonin is the most important

Table 1. Most common neuroendocrine tumors and their markers*

| Tumour | Marker |
|--|---|
| Carcinoid tumour | urinary 5-HIAA, serum CgA |
| Nonfunctioning carcinoid tumour | serum CgA, serum NSE |
| Insulinoma | serum insulin, serum c-peptide, serum proinsulin, serum CgA |
| Nonfunctioning pancreatic NET | serum (PP) pancreatic polypeptide, serum CgA, serum NSE |
| Gastrinoma | serum gastrin, serum CgA |
| Pheochromocytoma, paraganglioma | urinary/plasma metanephrine & normetanephrine, serum CgA, serum NSE |
| Glucagonoma | serum glucagon, serum pancreatic polypeptide, serum CgA |
| Medullary thyroid carcinoma | serum calcitonin, serum CEA (carcinoembryonic antigen), serum CgA |
| Parathyroid tumour | serum parathormone |
| Neuroblastoma | serum NSE, serum CgA |
| Small cell lung cancer | serum NSE, serum CgA |
| Large cell lung cancer | serum NSE, serum CgA |

*: Markers are aligned according to their clinical importance, NSE: Neuron-specific enolase, CgA: Chromogranin A

marker in medullary thyroid carcinoma, insulin in insulinoma, and catecholamines in pheochromocytoma. In functional NETs, high CgA levels can be measured particularly in patients with large tumor burden or metastasis (8,11). Hence, in such functional NETs, CgA can be used as an auxiliary marker to the specific markers. Renal failure, liver failure, some carcinomas other than NETs (prostate, breast, thymus, uterus, colon), inflammatory bowel diseases, Parkinson's disease, pregnancy, chronic gastritis, untreated hypertension, cardiac insufficiency, acute coronary syndrome, untreated hyperthyroidism, systemic rheumatoid arthritis, chronic bronchitis, chronic obstructive pulmonary disease, somatostatin analogues, and proton pump inhibitors (PPIs) can affect the measurement of serum CgA values. It has been suggested that CgB can be a complement to CgA in many of these situations (12). It is important to remember that plasma CgB levels are raised particularly in metastatic NETs and it seems that more and larger studies should be done about CgB. Additionally, another suggestion is when a borderline or doubtful value of CgA is observed, before proceeding to the other studies for diagnosis, repeating the CgA assay with the addition of the measurement of NSE plasma level and particularly of urinary 5-HIAA level (17). Measurements of CgA levels should be performed by the same method of assay, because methods of CgA assay have not been standardized yet and can cause very different results in the same blood sample. Besides, cut-off values may also differ due to methods therefore, assay methods should be taken into consideration when evaluating the CgA results (18).

5-Hydroxyindoleacetic Acid

Serotonin is metabolized mainly in the liver via enzymatic conversion by monoamine oxidase-A to 5-HIAA and there after, circulating 5-HIAA is excreted to urine (19,20). Although analysis of serotonin level has not been frequently performed, 24-hour urinary 5-HIAA level has commonly been used to determine the excess serotonin levels (5,8,21). 5-HIAA level can be measured by liquid chromatography (HPLC) method. Serotonin, also known as 5-hydroxytryptamine, is a neuroamine and can be found at many sites of the body, mostly in the gastrointestinal tract (enterochromaffin cells), brain, and platelets. Serotonin is involved in brain functions, gut movements, bone formation, blood pressure regulation, blood clotting, and vasoconstriction. Many tissues which contain the special granules of serotonin also have the features of neuroendocrine cells. Thus, tumors that take origin from them are generally NETs, particularly carcinoid tumors.

In that regard, urinary 5-HIAA level is the most important marker of carcinoid tumors and carcinoid syndrome. Urinary 5-HIAA levels higher than 25 mg/day are significant for the diagnosis of carcinoid tumors. 5-HIAA levels are also associated with the tumor size, response to treatment and prognosis in carcinoid tumors (22). Indeed, carcinoid syndrome has the features related to excess secretion of serotonin, kallikrein, histamine, tachykinins (neurokinin A and substance P), and others (19). Though the prominent product seems to be serotonin, some patients with carcinoid syndrome may have low or normal levels of 5-HIAA (14). Carcinoid syndrome presents with dry flushing (90%), diarrhea (70%), nausea-vomiting with abdominal pain (40%), valvular heart disease (40-45%), telangiectasia (25%), bronchial constriction (15%), and pellagra (5%). The most encountered clinical feature is dry (without sweating) flushing of the skin, generally on the head and neck (10).

A life-threatening complication of Carcinoid syndrome, carcinoid crisis, may have features such as flushing, fluctuating blood pressure, tachycardia, arrhythmias, bronchospasm, and unconsciousness. It may rarely occur spontaneously, but more usually, it is triggered by preoperative anaesthetic induction, handling of the tumor intraoperatively or other severe invasive therapeutic procedures (6). Hence, it is essential to initiate the treatment with short-acting somatostatin analogues at least two days before invasive procedures.

The interfering foods and drugs have to be forbidden before the 5-HIAA assay (Table 2) (10,16). It is very important to instruct the patients about the procedure of assay and dietary restrictions. Patients have to be routinely recommended to make a diet that does not contain certain foods and to stop drugs 3 days before the assay. It is noteworthy that, urine container needs to be acidified at first. In addition, urine samples should be collected in a single container for 24 hours and refrigerated during that time.

Provocative tests, such as pentagastrin and calcium infusion test used to clarify suspicious carcinoid syndromes must be carefully performed; because dangerous side effects due to carcinoid crisis may develop in patients with NET (8,23). Short-acting somatostatin analogues must immediately been administered if carcinoid crisis occurs.

More than 70% of midgut (jejunum, ileum, right colon, and appendix) and 10-35% of stomach and respiratory system NETs secrete serotonin (4). Importantly, when all carcinoid tumors of the gastrointestinal tract are taken into consideration together, most of them do not lead to Carcinoid syndrome. Actually, carcinoid syndrome occurs in less than 10% of patients with

Table 2. Foods, drinks, and drugs which interfere with the results of 5-HIAA assay

| | |
|--|--|
| Foods and Drinks Lead to False Positive Results | Fruits in general, banana, kiwis, avocado, pineapple, plums, nuts, tomato, aubergine, black olives, spinach, broccoli, cauliflower, cheese, red wine, coffee, tea, chocolates, soupmix, custard, hot dogs, figs, grapefruit, and honeydew melon |
| Drugs Lead to False Negative Results | Somatostatin analogues, levodopa, methyl dopa, heparin, isoniazid, monoamine oxidase inhibitors, methenamine, tricyclic antidepressants, phenothiazines, aspirin, ethanol, and corticotrophin (ACTH) |
| Drugs Lead to False Positive Results | Paracetamol, naproxen, phenacetin, fluorouracil, testosterone, methysergide, acetanilide, reserpine, atenolol, pindolol, oxprenolol, nicotine, ephedrine, glyceryl guaiacolate (found in many cough syrups), diazepam, methocarbamol, and caffeine |

carcinoid tumors. The reason for this event is the metabolization of circulated serotonin to 5-HIAA by the liver. Carcinoid syndrome can occur when liver, retroperitoneum or bone metastases are present. The syndrome may also occur when the carcinoid tumor is located in the bronchi, ovary, kidney, testes or thymus, not within the gastrointestinal tract (6,19). It is noteworthy that urinary 5-HIAA levels are elevated in cases that NET secretes serotonin, but it converts to 5-HIAA by the liver. As a result, measurement of urinary 5-HIAA levels permits the detection of approximately 85% of patients with carcinoid tumors.

On the other hand, in most of the carcinoid tumors, CgA levels are also elevated (3,4,5). 5-HIAA has a sensitivity and specificity of 100% and 73%, respectively, whereas CgA has 98.4% and 62.9% to detect the carcinoid tumors which are functioning (3). On the other hand, CgA is certainly more useful than 5-HIAA for the carcinoid tumors which are non-functioning (5). The carcinoid tumors of the foregut (stomach, duodenum, biliary system, pancreas, and bronchus) secrete less amounts of serotonin when compared to midgut tumors, while tumors of the hindgut (left colon and rectum) rarely secrete serotonin (16). Indeed, carcinoid tumors which are located in the left colon and rectum very rarely secrete serotonin and they usually present with a metastatic disease. CgA is more useful than 5-HIAA in carcinoid tumors of the hindgut which rarely secrete serotonin. Furthermore, circulating α and β -subunits of hCG and pancreatic polypeptide levels may also raise in gastrointestinal carcinoid tumors (6).

Insulin

Insulinomas are the second most frequent NETs after carcinoid tumors. Approximately 15% of NETs are insulinomas. They are generally detected earlier than other NETs because of the severe symptoms of hypoglycemia. Insulinomas are usually single tumors (except in patients with MEN II), benign tumors (90%), generally smaller than 1 cm, and almost always (>99%) located anywhere within the pancreas (10).

Although, 72-hour fast is the gold standard for the diagnosis of insulinoma, performing this test is not necessary in most patients, because only several hours of fasting are enough to detect severe hypoglycemia. Insulin values of ≥ 6 $\mu\text{U/L}$ measured by enzyme-linked immunosorbent assay (ELISA) or immunoradiometric assay (IRMA) method (≥ 3 $\mu\text{U/L}$ if immunochemiluminometric assay-ICMA is used), while blood glucose level is less than 40 mg/dL, are highly compatible with insulinoma. An insulin/glucose ratio of ≥ 0.3 and C-peptide levels of 200 pmol/L have also been found in almost all patients with insulinoma (16). On the other hand, in case of high insulin levels with low C-peptide levels, self administration of insulin should be thought. However, abuse of sulfonylureas is more difficult to diagnose because both serum insulin and C-peptide levels are elevated. Measuring the metabolites of sulfonylureas is the unique way to detect abuse of sulfonylureas. Additionally, serum proinsulin values of greater than 5 pmol/L with glucose levels of less than 40 mg/dL are compatible with insulinoma. Besides, a proinsulin level accounting more than 40%

of total insulin is highly suspicious for malignant insulinoma. As well known, for about 10% of insulinomas are malignant and 10% of them are located elsewhere than in the pancreas.

Finally, all the above mentioned tests for the diagnosis of insulinomas can also be used for nesidioblastosis with the same diagnostic levels. Differential diagnosis of insulinoma and nesidioblastosis can only be made by the pathological examination of the removed pancreatic tissue.

Conclusion

In conclusion, as the awareness about NETs is increasing, it is also crucial to raise the level of knowledge about their biomarkers. Using biomarkers more commonly and properly will lead to more frequently diagnosed and more correctly treated NETs. In addition, although the most frequently used markers in the clinical practice are CgA and 5-HIAA, all NET markers have special clinical significances in NETs.

Conflicts of Interest

There are no conflicts of interest.

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