Diagnostic value of chromogranin A as a biomarker of neuroendocrine tumors

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Abstract

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies that arise from neuroendocrine cells that are dispersed throughout the body, especially in gut and lung. Although NETs present a diverse group of malignancies considered to be rare, recent large population-based studies data are indicating a significant increase in both incidence and prevalence.

The diagnosis of NETs is a complex and multimodal process, based on clinical symptoms, laboratory biochemical markers, radiological and nuclear imaging and histological confirmation. In those conditions the appropriate use of biomarker testing may be helpful in making a diagnosis of a NET.

Plasma chromogranin A (CgA) is the most important general tumour marker and it should be measured in every patient with a suspected NET. CgA is useful in evaluation of tumor presence and spread of disease, and also in disease recurrence, prognosis and therapy.

Keywords: chromogranin A, neuroendocrine tumors, plasmatic biomarkers.

Neuroendocrine tumors (NETs)

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies that belong to the family of solid malignant neoplasms.

Unlike classical neuroendocrine neoplasms that arise in native endocrine glands, these tumors arise from neuroendocrine cells that are dispersed throughout the body, especially, gut and lung and more rarely in other sites, including prostate and ovary (1).

Many NETs are characterized by their ability to store and secrete different peptides and neuroamines causing specific clinical syndromes, whereas others that are not associated with a distinct hormonal syndrome may be asymptomatic and silent (2).

The understanding of GEP NETs has remained rudimentary since Oberndorfer in 1907 first commented on tumors of small intestine. He initially considered them benign and termed them carcinoid (cancer-like) before detailing their malignant behavior in 1929.

Most GEP NETS that arise from gut or bronchopulmonary system are commonly called carcinoid tumors where carcinoid is a generic term for a characteristic syndrome that results from intermittent release of bioactive amines into the systemic circulation.

High prevalence, increased incidence

Although NETs present a diverse group of malignancies considered to be rare, recent large population-based studies data are indicating a significant increase in both incidence and prevalence during the last few decades.

In contrast to the overall incidence of malignancies, epidemiologic data survey from the Surveillance, Epidemiology, and End Results (SEER, 1974-2005) demonstrate a significant increase in NETs incidence and prevalence.

Current figures indicate in 2004 an incidence of 5.25 new cases of NETs per 100 000 people per year and a prevalence of 35 per 100 000 people (3).

While the true cause of the rising incidence is unclear, it might be related to some possible contributing factors as increased awareness among physicians, better diagnosis and treatment, improvement of diagnostic techniques, changes in dietary habits, environmental factors, and use of certain medications (including proton pump inhibitors). Thus, the perceived increase in incidence may not be a real change in the incidence of the disease.

According SEER the majority of NETs occur in the GI tract (around 75%) and the bronco pulmonary system. Within the GI tract, most NETs occur in the small intestine, rectum, stomach and pancreas (4).

NET Nomenclature

Because of this heterogeneity, different naming conventions for NETs have been used for years.

Neuroendocrine neoplasms have been classified by site of origin, foregut, midgut, hindgut tumors, pancreatic NETs are considered to originate in the foregut.

Distal tumors include NETs in other locations such as the ear, heart, and ovaries (5).

In 2010, the World Health Organization (WHO) updated its classification of NETs dividing into 2 clinically distinct pathologic classes: well- and poorly differentiated.

Well-differentiated NETs can be classified in two grades (G1 and G2), depending on proliferation and histology. WHO 2010 guidelines apply the term "carcinoid" to grade 1 NETs only. Mitotic rate and proliferative index of the tumor (used more widely in Europe than it is in the United States to assess proliferation) are the most important features used for tumor grading (6).

The SEER program database also uses a "localized," "regional," and "distant" system to stage disease.

But the WHO, European Neuroendocrine Tumor Society and American Joint Committee on Cancer (AJCC) classification systems reflect the widespread recognition that NETs should be staged using TNM criteria: primary tumor (T), lymph node involvement (N), and distant metastasis (M) (7,8).

NETs are also defined as 'functional' or 'non-functional' according to the presence of associated secretory symptoms.

Functional NETS, release a variety of vasoactive peptides and amines resulting in onset of systemic symptoms termed Carcinoid Syndrome (which is the primary clinical manifestation in 8-35% of NETs patients) (9). These symptoms are often nonspecific and can be easily mistaken for those of other conditions.

Some functional NETS, release hormones or peptides, causing characteristic hormonal syndromes, such as insulin, gastrin, glucagon, vasoactive intestinal polypeptide (VIP).

Non-functional NETs are not associated with Carcinoid Syndrome or other hormonal syndrome, so are more difficult to detect and the associated symptoms are related to increasing mass and/or metastases (e.g., obstruction, pain, bleeding) (10).

Diagnosis of NETs: Late

Neuroendocrine tumors are often very slow growing. The primary tumor is usually small and clinical symptoms are often absent until metastasis has occurred.

Unfortunately, NETs are often not diagnosed before they metastasize and 50% of patients with NETs have metastatic disease at diagnosis.

Initial metastases are usually noted in regional lymph nodes, then in the liver and finally in distant sites such as bone (11).

NETs are tumors with quite diverse and not characteristic symptomatology, which in some cases is completely absent. Their high metastatic ability when they are still small in size makes their early diagnosis essential. A definitive diagnosis is typically delayed and sometimes the correct diagnose is made only some months before patient's death (12).

The diagnosis of NETs is a complex and multimodal process, based on clinical symptoms, laboratory biochemical markers, radiological and nuclear imaging and histological confirmation.

In those conditions the appropriate use of biomarker testing may be helpful in making a diagnosis of a NET, even in the absence of a secretory syndrome. A variety of generalized and specific biochemical tests are available for symptomatic patients, which can assist with the initial diagnosis and assessment of required treatment, and may offer prognostic information (13-15).

But Plasma CgA is the most important general tumour marker and it should be measured in every patient with a suspected NET (16-19).

Granins

The study of granins was initiated over 30 years ago, but during the last 15 years there has been an increase of studies related to the structure, function and their clinical importance as tumor biomarker (20,21). Granins are a unique group of acidic, secretory soluble, single chains glycoproteins (included chromagranis and secretogranins). They are produced, stored and release from vesicles which are present throughout the neuroendocrine system and in a variety of neurons.

The granins family consist of: Chromogranin A which was first isolated from chromaffin cells of the adrenal medulla (20,21); Chromogranin B initially characterized in a rat pheochromocytoma cell (22); Secretogranin II (sometimes called chromogranin C), which was originally described in the anterior pituitary (23); Secretogranin III (24) (or 1B1075); Secretogranin IV (or HISL-19) (25); Secretogranin V (or 7B2) (26); Secretogranin VI (or NESP55) (27).

Chromogranin A

Chromogranin A (CgA) is the first and best studied in the granin family. It is the main granin in the composition of secretory granules of neuroendocrine cells.

CgA is a highly hydrophilic acidic glycoprotein, composed from 439 amino acid residues, with 49 kD molecular mass and gene located on chromosome 14.

The intracellular functions of CgA: The precise function of CgA remains unknown, but it is thought to be involved in intracellular packaging of peptide, intracelular stabilisation of hormone vesicles, regulated pathways of secretion, modulation of

proteolytic processing, regulation of post-translational processing of hormones.

The extracellular functions of CgA: CgA is produced as prohormon and secreted by the regulated secretory pathway from neuroendocrine cells or neurons, tissue specific proteolysis giving rise to bioactive peptides with autocrine, paracrine and endocrine activities (28).

The biologically active peptides deriving from CgA are:

- Pancreastatin, which elevates blood glucose by inhibiting glucose-stimulated
- insulin release from pancreatic islet beta cells (29,30).
- Vasostatin, which inhibits vasoconstriction in isolated human blood vessels and modulate the adhesion of fibroblasts and coronary-artery smooth muscle cells (31).
- Catestatin, another fragment of chromogranin A, inhibits the release of catecholamines from sympathoadrenal chromaffin cells by blocking the neuronal nicotinic cholinergic receptor, which is the physiologic trigger for secretion (32).

Prochromacin and Chromacin with antibacterial and antifungal activities (33).

Chromogranin A: Clinical use

As CgA is produced by all types of neuroendocrine cells, it serves as a highly sensitive neuroendocrine cell bio-marker. Numerous studies have established that granins can be detected in an array of endocrine, neuroendocrine and neuronal tumors, from which they are secreted into the bloodstream (34,35).

According to many scientific studies, CgA plasma level is a very useful biomarker in NETs. It gives information and is correlated with: Tumor presence, progression and volume. It is also correlated with patient survival, prognosis and therapy.

CgA: Tumor presence and spread of disease

Elevated circulating CgA levels have been demonstrated in plasma of patients with various hormone-secreting or non-hormone secreting NETs.

CgA can also aid in the diagnosis of clinically silent, or "nonfunctioning," neuroendocrine tumors, which are very difficult to be diagnosed (36).

Therefore, CgA is widely used as diagnostic tool and is recommended by most societies (ENETS, UKINETS, NANETS) as a general serum marker for NETs (37,38).

In a study performed by Nobels, who is one of the best known of the field, serum concentrations of the CgA, were determinate in 211 patients with neuroendocrine tumors and compared to levels of a control group, consisting of 180 patients with nonendocrine neoplasms (39). In this study, plasmatic levels of CgA results higher in patients group compare with control group. The highest elevations of CgA were observed in subjects with carcinoid tumors, in subjects with nonfunctioning pancreatic islet cell tumor, medullary thyroid carcinoma, pheochromocytoma, paraganglioma, small cell lung carcinoma, gastrinoma, and Merkel cell tumor.

The sensitivity and specificity of circulating CgA in any NETs vary between 70% and 95%. The highest accuracy has been observed in tumors characterized by an intense secretory activity, but its specificity and sensitivity remain very high also in non-functioning tumors.

According Campana and Notling Study (40,41), in the disease-free patients CgA levels were lower than the levels found in patients at any other stage of endocrine neoplastic disease. In this study were observed higher CgA levels in patients with diffuse disease compared to patients with local or hepatic disease. In Notling Study NETs patients affected by liver metastases showed significantly higher median CgA values than those without liver metastases. Also in some studies are detected significantly higher plasma CgA levels among patients with multiple ($\geq$5) liver metastases than in those with only few ($\leq$5) liver metastases, or lymph node metastases alone (42). A significant positive relation between the plasma levels of CgA and the tumor mass in NETs, has been also demonstrated.

CgA: Disease recurrence, prognosis and therapy

According Welin study (43) elevated CgA was the first marker to become pathologically elevated in 85% of patients with NETs recurrence.

According to this study, Welin recommends to avoid unnecessary and costly examinations in asymptomatic patients, suggesting that follow-up should comprise measurements of P-CgA twice a year and annual ultrasonography until P-CgA is elevated or clinical symptoms occur.

CgA as tumor biomarker may also have prognostic implications where high levels indicate a worse prognosis (44,45).

Yao study in 2010, evaluate the prognostic value of CgA and NSE in patients with pNETs treated with everolimus. In advanced cases submitted to therapy, a clear relationship was found between changes in CgA levels and disease response after therapy (46). This bio marker decreased in all patients showing tumor shrinkage after treatment, increased in the great majority of patients showing progressive disease, and did not change in most cases depicting disease stabilization (47). Early CgA responses may be a predictive of progression-free survival benefit in patients with advanced pancreatic neuroendocrine tumors (pNET).

CgA levels interpretation and pitfalls

There are a number of other unrelated conditions with neuro-endocrine tumor that may affect the levels of plasma CgA and can influence the interpretation of the test values.

Renal impairment is one of the most important. All the patients with chronic renal failure presented very high levels of CgA, thus suggesting that serum creatinine should always be measured concomitantly with plasma CgA (48).

False elevation of CgA are observed due to the use of proton pump inhibitors or histamin 2 receptor antagonists (e.g., omeprazole, lansoprazole, pantoprazole) (49). CgA levels elevate and directly correlate with disease severity in congestive heart failure; patients with New York Heart Association (NYHA) Class IV heart failure exhibit CgA elevations ~7.6-fold greater than normal (50). False positive elevation of CgA may also occur in: chronic atrophic gastritis, hepatic failure, inflammatory bowel disease, parkinson disease, untreated hypertension, pregnancy, steroid treatment or glucocorticoid excess, hyperthyroidism.

There is no universal calibration standard for serum chromogranin A assays. Different chromogranin A assays, which use different antibodies or antibody combinations, will display different cross-reactivity with the various chromogranin A fragments. Therefore, reference intervals and individual patient results differ significantly between different chromogranin A assays and cannot be directly compared. Serial measurements should be performed with the same assay, or if assays are changed, patients should undergo a new baseline measurement (51).

Conclusion

NETs are not that rare and should receive more specialized attention, although in recent years significant progress is being made in NETs diagnosis and treatment.

CgA, recommended by most societies (ENETS, UKINETS, NANETS) as a general serum marker for NETs, is the best circulating neuroendocrine marker available up to now. It provides a more sensitive assessment compared with other biomarkers. Its clinical application involves all differentiated NETs and is a useful tool in NETs presence progression volume Survival Therapy. Sensitivity of elevated CgA varies according to NETs type and volume.

Other benign conditions can also cause increased levels and influence of the test values interpretation. Although CgA serve as a good clinical biomarker, we are in deep need of new biomarkers for detection of early recurrence after surgery with curative intent, but also early diagnosis. Besides circulating tumor markers, some new tissue markers are also in progress, as well as studies on

circulating tumor cells that might provide important information for treatment decisions in the future.

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