Chromogranin A – unspecific neuroendocrine marker. Clinical utility and potential diagnostic pitfalls

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Abstract

Chromogranin A, despite a number of limitations, is still the most valuable marker of neuroendocrine tumors (NETs). Granins belong to the family of acidic proteins that constitute a major component of secretory granules of various endocrine and neuroendocrine cells, which are components of both the classical endocrine glands and the diffuse neuroendocrine system. These cells are a potential source of transformation into neuroendocrine tumors. The awareness of potential causes influencing the false results of its concentrations simplifies diagnosis and treatment. One of the disadvantages of this marker is its non-specificity and the existence of a number of pathological processes leading to an increase in its concentration, which often results in confusion and diagnostic difficulties. The molecular structure is characterized by a number of sites susceptible to the proteolytic activity of enzymes, resulting in the formation of a number of biologically active peptides. Presumably they act as precursors of active proteins. Chromogranin expression correlates with the amount of secretory vesicles in neuroendocrine cells. The peptide chain during biochemical changes becomes a precursor of biologically active proteins with a wide range of activities. There are a number of commercially available kits for the determination of chromogranin A, which differ in methodology. We present the evaluation of chromogranin A as a marker of neuroendocrine tumors in clinical practice and the possible factors that may affect the outcome of its concentration.

Key words: chromogranin A, neuroendocrine tumors.

Introduction

The growing interest in neuroendocrine tumors, which are interdisciplinary diseases, is associated with an increase in their detection in recent years. Due to their usually indolent character we are dealing with a metastatic proliferative process at the time of diagnosis. Therefore, as in other neoplasms, attempts are made to use biochemical markers that could serve as a valuable diagnostic tool and indicator of response to treatment or recurrence of the disease. The marker for neuroendocrine tumors is chromogranin A, which often in the absence of other biochemical markers of the disease is a useful factor in both the diagnosis and monitoring of disease. One of the disadvantages of this marker is its non-specificity and the existence of a number of pathological processes leading to an increase in its concentration, which often results in confu-

sion and diagnostic difficulties. In this review, we would like to present the current state of knowledge about the usefulness of this marker in neuroendocrine tumors and provide a number of conditions that can give false positive results.

General characteristics

Granins belong to the family of acidic proteins that constitute a major component of secretory granules of various endocrine and neuroendocrine cells, which are components of both the classical endocrine glands and the diffuse neuroendocrine system. These cells are a potential source of transformation into neuroendocrine tumors. The family consists of 8 granin proteins: chromogranin A, B, C (secretogranin II), secretogranin III, IV, V, VI, and VEGF. Granins potentially play an essential role in the creation, maturation and exocytosis of secretory vesicles containing biologically active neuropeptides, neurotransmitters and hormones. Their molecular structure is characterized by a number of sites susceptible to the proteolytic activity of enzymes, resulting in the formation of a number of biologically active peptides. Presumably they act as precursors of active proteins.

Chromogranin A (CgA) was the first identified representative of granins, and derives its name from the spot of primary detection (adrenal medulla chromaffin vesicles containing catecholamines) [1, 2]. It is encoded by the gene CHGA/CgA located on chromosome 14. Chromogranin expression correlates with the amount of secretory vesicles in neuroendocrine cells. The peptide chain during biochemical changes becomes a precursor of biologically active proteins with a wide range of activities. From the 439-amino acid chain of chromogranin A there arise a number of peptides:

- vasostatin I – exhibiting antiadrenergic activity [3],
- parastatin – inhibiting secretion of parathyroid hormone in response to low levels of calcium [4],
- pancreastatin – showing a strong inhibitory effect on insulin secretion induced by increasing concentration of glucose in the blood [5],
- catestatin – inhibiting secretion of catecholamines from the chromaffin cells [6].

To date, knowledge about the other products of chromogranin A proteolysis (vasostatin II, chromostatin, GE-25, EC-14) is scant and their biological effect is not certain [7]. Interestingly, proteolysis of chromogranin appears to be organ specific. For example, pancreastatin found in the α cells of the pancreas is absent in adrenal medulla chromaffin cells [8].

Methods for determination of chromogranin

There are a number of commercially available kits for the determination of chromogranin A, which differ in methodology. Three diagnostic techniques are available: enzyme-linked immunosorbent assay (ELISA), immunoradiometric assay (IRMA) and radioimmunoassay (RIA). There is no standardization for any of the techniques: different studies use different antibodies, which in turn react with different antigenic epitopes on the surface of the protein chain. Determination of CgA by different techniques leads to significant differences in results, with varying effects on sensitivity and specificity. Currently there is no universal, worldwide accepted diagnostic technique; thus caution is recommended when trying to compare the results from different research centers. Chromogranin can be measured from plasma or serum. It has been reported that plasma chromogranin tends to be markedly higher than that determined in the serum [9]. There are many studies comparing the sensitivity and specificity of available diagnostic methods. Stridsberg *et al.* compared all 3 methods. For IRMA sensitivity was 67% and specificity 96%, for ELISA sensitivity was 85% and specificity 85%, and for RIA sensitivity was 93% and specificity 85%, suggesting that the best compromise between sensitivity and specificity is the use of RIA [10].

Chromogranin A – potentially false positive results

Because of wide spectrum chromogranin A secretion, together with other regulatory proteins, there are several causes of elevated chromogranin unrelated to neuroendocrine tumor. In clinical practice, the most common causes of false (non-NET) CgA results is the use of proton pump inhibitors, cases of atrophic gastritis and impaired kidney function. The majority of false positive results are about 2–4 times higher than the upper reference range, but a significant number of these results may reach up to 5–20 times higher than the upper reference range [11].

Gastric disorders

Elevated CgA levels are observed in cases of atrophic gastritis or during treatment with proton pump inhibitors (PPIs) and other acid suppressive medications. Lack of gastric acids engenders hypergastrinemia due to no negative feedback for gastrin, which in turn stimulates the growth of enterochromaffin cells to secrete CgA. Therefore, we obtain elevated circulating CgA. The PPI therapy may increase CgA concentration just 5 days after the first intake and leads to CgA 5–10 times higher than the upper reference range, results often seen in patients with early stage NET [12]. To prevent any impact on the value of CgA by PPIs, a drug should be discontinued at least 7 days before the test. It should also be remembered that the longer

PPI therapy lasts, the longer is the time needed for the normalization of CgA concentration. Histamine type-2 receptor antagonists (H2RA) may also have an effect on the increase of the marker. It is suggested to discontinue these medications for at least 24 h before the scheduled CgA examination.

Impaired kidney function

Elevated CgA also occurs in the case of impaired kidney function due to reduced renal clearance. The higher the degree of renal failure, the higher the CgA concentration, and the result may reach the level found in neuroendocrine tumors [13]. Before interpreting the result of CgA as a marker of NET, renal function should be evaluated carefully to rule out the potential impact on the concentration of CgA. Evaluation of CgA as a marker of NET in the case of end stage renal disease is impossible.

Heart diseases

In a study of 160 patients with chronic heart failure, CgA concentration was significantly higher than in healthy volunteers. CgA levels correlated with the intensity of heart failure defined on the basis of the NYHA scale. Patients in the fourth grade showed the highest concentration of circulating CgA. It was further found that the concentration of chromogranin A is an independent marker of mortality [14]. Interestingly, in patients with chronic heart failure, CgA levels did not correlate with the concentration of the hormones that are involved in the pathophysiological basis of the disease, including catecholamines and components of the renin-angiotensin-aldosterone system [15]. CgA concentration in this case correlated with the concentration of brain natriuretic peptide (BNP) [16, 17]. Elevated chromogranin A is also observed in cases of acute coronary syndromes, where a high concentration of the peptide significantly worsens the prognosis [18]. Circulating CgA seems to reflect inflammation and cardiac overload rather than activation of the autonomous nervous system. In this case, CgA showing a negative inotropic and lusitropic effect plays a protective role in preventing excessive activation of the heart muscle in response to stress factors [16].

Hypertension

There is a high concentration of CgA in the case of untreated hypertension, and CgA levels may correlate with the severity of hypertension in conjunction with increased adrenergic activity.

Rheumatoid diseases

In rheumatoid arthritis, the concentration of CgA correlates with the concentration of the receptors for tumor necrosis factor-α (TNF-α), and treatment with anti-TNF-α impairs this correlation, suggesting a connection between these two molecules. Interestingly, patients with generalized disease manifestations showed unusually high concentrations of CgA, which were sometimes even higher than those observed in patients with neuroendocrine tumors, compared with patients with disease limited only to joints. The CgA concentration seems to reflect generalized inflammation and, by its derivative vasostatin 1, exhibits a protective effect on the endothelium by inhibiting inflammation mediated by TNF-α [19]. Elevated CgA is also observed in other rheumatoid diseases such as systemic lupus erythematosus.

Inflammatory bowel disease

Many patients with neuroendocrine tumors derived from the midgut are initially erroneously diagnosed with irritable bowel syndrome, sometimes even a few years before the correct diagnosis. There are reports of an increased concentration of CgA in irritable bowel syndrome and inflammatory bowel disease. Therefore evaluation of CgA is not valuable as a screening test in the evaluation of uncertain cause diarrhea [20]. Approximately 50% of patients with inflammatory bowel diseases tend to have elevated CgA, especially in the case of the active phase of the disease [21].

Other causes

Worthy of note is the fact that in both healthy individuals and patients with neuroendocrine tumors CgA increases under the influence of food intake and exercise. Maximum CgA concentrations are observed 30–90 min after a meal and reach 2–3 times the upper reference range [22]. Therefore it is recommended to measure CgA after rest and fasting. Differences in concentration of CgA measured day by day can be up to 20%, and this phenomenon is observed in both healthy volunteers and patients with NET [23]. For other potential causes of false-positive results of chromogranin A see Tables I and II.

Chromogranin A and neuroendocrine tumors

The CgA is secreted by a number of neuroendocrine tumors, which broadly include: pheochromocytoma, medullary thyroid carcinoma, parathyroid adenomas, pulmonary neuroendocrine tumors including small cell lung cancer, and finally gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Nobels *et al.* evaluated the usefulness of determining the concentration of chromogranin A as a marker of tumors in different disease entities [24].

The concentration of chromogranin A was elevated in 100% of cases of gastrinomas, in 89% of

Table I. Factors affecting the concentration of chromogranin A

Factor	False positive results
Diseases of the cardiovascular system	Hypertension, heart failure, acute coronary syndrome
Renal diseases	Impaired kidney function/renal insufficiency
Diseases of the alimentary tract	Chronic atrophic gastritis, inflammatory bowel diseases, irritable bowel syndrome, pancreatitis, chronic hepatitis, liver cirrhosis
Non-neuroendocrine neoplasms	Prostate cancer, ovarian cancer, breast cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, hematological malignancies
Inflammatory diseases	Systemic rheumatoid arthritis, systemic lupus erythematosus, COPD
Endocrine disorders	Pheochromocytoma, hyperparathyroidism, hyperthyroidism, medullary thyroid cancer, pituitary tumors (except prolactinomas), hypercortisolemia
Medications	Proton pump inhibitors, histamine type-2 receptor antagonists
Other	Food intake or strenuous exercise before the test

Table II. Metabolism of chromogranin A. Neuroendocrine and non-neuroendocrine diseases with elevated chromogranin A concentration in serum

Neuroendocrine diseases	Non-neuroendocrine diseases
1. Pheochromocytoma	1. Renal failure
2. Neuroblastoma	2. Chronic atrophic gastritis type A
3. Medullary thyroid carcinoma	3. Crohn's disease, ulcerative colitis
4. Pituitary adenomas (acromegaly)	4. Rheumatoid arthritis
5. Primary hyperparathyroidism	5. Parkinson's disease
6. Hormonal activity of fetal placenta	6. Steroid treatment
7. Hypercortisolism	

pheochromocytomas, 80% of neuroendocrine tumors of the small intestine, 69% of non-functioning pancreatic neuroendocrine tumors and in the case of medullary thyroid cancer concentrations above the reference range were recorded in 50% of cases. What is important, in 7% of cases in the control group elevated CgA was also observed.

Chromogranin A and non-neuroendocrine neoplasms

Elevated chromogranin in cases of prostate cancer shows neuroendocrine differentiation of tumor tissue, which is associated with progression, poor prognosis and resistance to hormonal therapy [25]. Elevated concentrations were also observed in the case of other types of cancer: breast cancer, cancer of the digestive gland, cancer of the female genital tract, hematological malignancies and cancers of the head and neck [26]. In studies assessing CgA levels in neoplasms other than neuroendocrine tumors and small cell lung cancer there was no difference between serum CgA and tumor size [27, 28]. These data are surprising because most tumor markers correlate with tumor size or progression of the disease. Markers are significantly higher in the case of disseminated neoplastic processes. This situation indicates that elevated CgA cannot be used to assess the severity or progression of the disease in tumors other than those of neuroendocrine origin.

Chromogranin A and gastroenteropancreatic neuroendocrine tumors

Chromogranin A concentration and staging

In general, the highest values of CgA and accuracy in the determination of CgA are observed the most frequently in tumors showing intense secretory activity, mainly neuroendocrine tumors of the small intestine, particularly causing carcinoid syndrome (midgut neuroendocrine tumors) [29]. Chromogranin A is significantly higher in the case of disseminated rather than limited neoplastic disease. An exception may be a gastrinoma, as here CgA is high even in the absence of metastases in the liver [30]. In the case of midgut tumors the comparison of CgA concentration and severity of disease was performed. Patients with multiple liver metastatic disease demonstrated a significantly higher concentration of CgA than patients with only a few lesions in the liver or lymph node metastases [31]. Satisfactory accuracy of CgA is also observed in hormonally inactive cases of neuroendocrine tumors [32]. The CgA is described as a prognostic marker for GEP-NET: high levels correlate with shorter survival and liver cancer bur-

den. Chromogranin A concentrations and sensitivity depend mainly on the spread of cancer. Arnold *et al.* reported that the accumulation of metastatic changes in the liver significantly increases the concentration of CgA. In addition, the appearance of metastases to lymph nodes in previously proven metastases in the liver did not cause a further increase in the value of CgA [33]. Moreover, Janson *et al.* observed a significantly higher CgA concentration in the case of multiple metastatic lesions in the liver (> 5) in comparison to the case of only a few metastases (< 5) or only lymph metastases [29]. Walter *et al.* reported that CgA levels are significantly elevated more frequently in the case of NET metastases compared to reduced cancer (74% vs. 51%) [34].

Chromogranin A and tumor primary location and grading

Taking into account the relationship between the tumor primary location and sensitivity of CgA, most data show higher sensitivity in the case of midgut neuroendocrine tumors compared with pancreatic neuroendocrine tumors [10, 30, 35, 36]. The highest values of CgA are observed in small intestine neuroendocrine tumors (up to 200 times above normal) and GEP-NETs occurring in MEN-1 syndrome (up to 150 times above normal). As regards the pancreatic neuroendocrine tumors, both functioning and non-functioning tumors reveal intermediate levels of CgA (up to 60–80 times the upper reference). In the case of Zollinger-Ellison syndrome connected with MEN1 syndrome, and in the case of type II and III gastric neuroendocrine tumors, values are up to 80–100 times higher than the upper reference range [37]. The sensitivity and specificity of CgA for different types of neuroendocrine tumors are in the range 60–100% and 70–100%, respectively, with the highest values observed in the case of serotonin-secreting neuroendocrine tumors (carcinoid tumors) [38, 39]. In the case of serotonin-secreting neuroendocrine tumors originating from the midgut, CgA concentration is an independent prognostic factor, because its concentration is correlated not only with the size of the tumor but also with the intensity of biological activity [40].

Chromogranin A as a prognostic factor

Chromogranin A concentration can be used as an indirect predictor of cancer. There is a correlation between the staging of the disease and concentration of CgA. As mentioned above, higher CgA is observed for metastatic disease compared to localized disease [41]. There are reports of a correlation between CgA and survival in neuroendocrine tumors. A concentration 3 times above the upper reference range at the time of diagnosis is a significant predictor of shorter survival (hazard ratio 2.6) in patients with pancreatic neuroendocrine tumors [42]. In the case of neuroendocrine tumors of the midgut, CgA level > 5000 µg/l was an independent predictor of shorter survival of patients, and comparing the results of > 5000 µg/l and < 5000 µg/l, the median survival was 33 months and 57 months, respectively [31]. Elevated CgA was associated with significantly shorter survival in the study of midgut tumors with liver metastases treated with a long-acting somatostatin analog, while no relationship between survival and concentrations of urinal 5-hydroxyindoleacetic acid (5-HIAA), the breakdown product of serotonin, was observed [43]. Worthy of note is the fact that the correlation between serum CgA and survival cannot be used generally in relation to GEP-NETs. Gastrinoma are associated with high levels of chromogranin A in serum, even in the absence of metastases in the liver, which is associated with the above-mentioned enterochromaffin cell stimulation by gastrin, in this case with non-negative feedback.

Chromogranin A and relapse of the disease

In a retrospective study of 56 patients with NET, the concentration of CgA was the first indication of the recurrence of the proliferative process after radically carried out surgery. It suggests that the periodic evaluation of CgA may be a more preferred method than repeated radiological procedures in a situation where we have delayed with complete tumor resection previously [44]. The concentration of chromogranin A correlates with the size and extent of cancer; thus its periodic measurement may be helpful in detecting potential recurrence of the disease. A study evaluating the usefulness of CgA in monitoring of radically treated neuroendocrine tumors showed that the increase in CgA is the first marker of recurrence of the disease, which occurs before changes in the concentration of urinal 5-hydroxyindoleacetic acid or radiologic recurrence [44].

The same study showed that in 86% of patients with elevated chromogranin A the recurrence of the disease was present subsequently (33 of 56 patients, at a median of 32 months). Another study showed that among patients with GEP-NETs of different locations, who experienced progression of the disease, elevated CgA concentrations were observed in 83% of cases, while in patients with liver metastasis progression this result was observed in 100% of cases [45].

Chromogranin A and response to treatment

In cases of radically operated neuroendocrine tumors originating from the midgut, CgA levels were recorded as both a diagnostic and early re-

lapse marker. Reduction of CgA concentration is used frequently as an indicator of response to treatment in clinical trials, in which the biochemical response is usually defined as a ≥ 50% reduction in the concentration of CgA [33, 44, 46]. It is assumed that the reduction of CgA by more than 50% may be a proof of the correct choice of treatment. Assuming that the concentration of CgA correlates with the size and number of malignancies, the concentration of CgA is theoretically expected to decrease if treatment is effective. The study by Nehara *et al*. provided data indicating the reduction of circulating CgA concentration after resection or cytoreduction of the neuroendocrine tumor [41]. In the case of the use of different non-invasive methods also a correlation between the response to treatment of GEP-NET and the concentration of CgA was noted. It occurred as a reduction or stabilization of its concentration [45, 47–49]. Reduction of CgA concentration was observed after successful treatment with radionuclide therapy [50] and after liver transplantation due to massive organ metastases [51]. Generally CgA determination may be a useful tool in monitoring the treatment of GEP-NETs, with the stipulation that an elevated CgA level before therapy was observed [23].

Chromogranin A in the case of somatostatin analog therapy

In patients treated with somatostatin analogs (SSA), the relationship between circulating CgA and tumor mass is not obvious. This is due to the ability of SSA to block the production and secretion of chromogranin A [52]. Chromogranin A concentration may correlate with tumor size, but care must be taken during interpretation of the results. Serial CgA measurements during follow-up should be performed at approximately the same intervals after the administration of a long-acting SSA.

Chromogranin A and other NET biomarkers

Chromogranin A can be regarded as an early model of neuroendocrine tumors originating from the foregut and midgut and seems to be a better marker of the disease than the assessment of urinal 5-HIAA and/or circulating serotonin concentrations. There is a stronger correlation between the concentration of CgA compared to 5HIAA with regard to the general condition and well-being of the patient, similar to the correlation between survival and the level of CgA, which makes CgA a recommended first-line marker for GEP-NETs [43]. Another advantage in favor of CgA is definitely an easier way to collect samples for tests, compared to 24-hour 5HIAA urine collection. It should be remembered that in order to avoid false positive results of 5HIAA urine concentration, a special diet excluding numerous sources of tryptophan, such as bananas, cheese, chocolate, tomato, etc., should be introduced. In a study in which 127 patients with neuroendocrine tumors were enrolled, CgA demonstrated superiority over 5HIAA urine concentration, circulating neuron-specific enolase (NSE) and carcinoembryonal antigen (CEA) as a tumor marker [45]. Although the specificity of both 5-HIAA and NSE was high (up to 100%), low sensitivity (35% and 33%, respectively) was observed. Comparing the data for CgA in this case, the specificity was 86% and sensitivity 68%. It is worth noting that CgA may be a marker for high sensitivity in the case of metastatic NET, but the concentration of 5-HIAA has the highest sensitivity in patients with the symptomatic hormonally active form of GEP-NET [37].

Chromogranin A potentially false-negative results

Chromogranin A concentration may be normal in the case of neuroendocrine tumors with a mild proliferative potential. These include the majority of neuroendocrine tumors of the appendix, which apart from a few cases are mostly benign tumors, which when totally excised do not require a follow-up after treatment. About 75% of insulinoma tumors are usually mild and CgA is usually not increased, but in this case the measurement of CgA may be a helpful indicator of tumor malignancy. Besides several typical lung carcinoids, duodenum and rectum low proliferative index tumors may not show elevation of circulating CgA [11]. Rapidly proliferating, poorly differentiated neuroendocrine tumors, which in many cases lose their characteristic structure and show a much smaller number of secretory vesicles, may also not release the marker, giving false negative results.

Although CgA is not a specific marker for particular neuroendocrine tumors, one of its derivatives, neuroendocrine secretory protein 55 (NESP 55), seems to be a specific marker of pheochromocytoma and pancreatic neuroendocrine tumors, neuroendocrine tumors which are not present in the gut [53]. However, so far this marker can be used only with immunohistochemical techniques, and it is impossible to use it as a circulating marker.

Other applications of chromogranin A

Chromogranin A assessment may be helpful for differentiating sources of high cortisol levels in the case of Cushing's disease between pituitary, adrenal and ectopic ACTH secretion by a neuroendocrine tumor. In the latter case, significantly higher levels of CgA compared to other cases are observed [54].

There is a statistically significant difference in the concentration of CgA comparing benign and malignant pheochromocytomas [55, 56]. The CgA concentrations in the case of malignant lesions were approximately 15 times higher compared to benign lesions. Also there was a positive correlation between CgA and tumor size in the adrenal gland [57, 58]. Patients with adrenal tumors derived from the adrenal cortex usually do not have elevated circulating chromogranin A levels (especially in the case of incidentalomas) [59]. Chromogranin A concentration correlates well with the production of catecholamines; therefore the determination of CgA is a complementary method to other laboratory tests in the diagnosis of pheochromocytoma such as 24-hour urine catecholamine collection. Determination of CgA concentration is an important tool in the differential diagnosis of pheochromocytoma as a cause of secondary hypertension [58].

Conclusions

Sensitivity of CgA as a marker of neuroendocrine gastro-entero-pancreatic tumors depends on the location of the original tumor [60, 61], metastatic cancer, especially liver metastases [23, 30, 62, 63], and laboratory methodology: determining cutoff CgA [10, 34, 41, 62] and the use of a particular method for detection of CgA [10, 36, 62]. The greatest value of CgA as a marker of the disease is achieved in the case of metastatic disease to the liver. It is believed that improvement of the diagnostic sensitivity of CgA can be achieved by combining the measurement of its concentration with another diagnostic technique, especially scintigraphy or PET/CT based on somatostatin and its receptors. It is estimated that determination of CgA concentration and performing receptor scintigraphy with somatostatin analogs increases the sensitivity to 93%, whereas sensitivity of each of these techniques performed separately is estimated at 60–80% [64]. During the attempt to interpret the result of chromogranin A, caution is recommended, bearing in mind the multitude of factors that may lead to both false positive and negative results.

Conflict of interest

The authors declare no conflict of interest.

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