

©Borgis

*Piotr Glinicki, Wojciech Jeske

Chromogranin A (CgA): structure, biological function, pre-analytical, analytical, and clinical aspects of its measurement in blood

Chromogranina A (CgA): budowa, funkcja biologiczna, przedanalizacyjne, analityczne i kliniczne aspekty oznaczania jej we krwi

Department of Endocrinology, Centre of Postgraduate Medical Education, Bielański Hospital, Warszawa
Head of Department: prof. Wojciech Zgliczyński, MD, PhD

Key words

chromogranin A, CgA, neuroendocrine tumours, NET

Słowa kluczowe

chromogranina A, CgA, guzy neuroendokryne, NET

Address/adres:

*Piotr Glinicki
Department of Endocrinology
The Centre of Postgraduate
Medical Education
Bielański Hospital
ul. Cegłowska 80, 01-809 Warszawa
tel. +48 (22) 569-02-93
fax +48 (22) 834-31-31
glinicki@cmkp.edu.pl

Summary

Chromogranin A (CgA) is a main nonspecific neuroendocrine tumour (NET) marker. Currently few commercial assays are available: RIA, IRMA, ELISA, CLIA, TRACE. There are many factors: *in vivo*, *in vitro* and coexisting diseases which can influence the CgA blood concentration. Elevated CgA levels in blood can be usually detected in: gastroenteropancreatic neuroendocrine tumours (GEP-NET), pheochromocytoma, neuroblastoma, MEN syndromes, bronchopulmonary NETs, medullary thyroid carcinoma, small-cell lung carcinoma, and some other very rare NETs. CgA measurement became a routine investigation in the diagnosis of GEP-NET, but is especially helpful in monitoring the effects of their treatment. CgA can be considered as a complementary investigation in the diagnostic procedure of pheochromocytoma. In patients with multiple endocrine neoplasia (MEN) investigation of CgA level may be used in monitoring eventual coexistence or appearance with time of carcinoid, pancreatic neuroendocrine tumour or pheochromocytoma.

Streszczenie

Chromogranina A (CgA) jest głównym, niespecyficznym markerem guzów neuroendokrynych (NET). Obecnie dostępnych jest kilka komercyjnych testów: RIA, IRMA, ELISA, CLIA, TRACE. Istnieje wiele czynników: *in vivo*, *in vitro* i współistniejących chorób, które mogą wpływać na stężenie CgA we krwi. Podwyższone stężenie CgA we krwi obserwujemy zwykle w: guzach neuroendokrynych przewodu pokarmowego (GEP-NET), *pheochromocytoma*, *neuroblastoma*, zespołach MEN, guzach neuroendokrynych oskrzeli, raku rdzeniastym tarczycy, raku drobnokomórkowym płuc oraz w innych rzadkich guzach NET. Pomiar stężenia CgA jest obecnie rutynowo stosowany w diagnostyce guzów GEP-NET, ale szczególnie jest on przydatny w monitorowaniu efektów leczenia. CgA może być dodatkowym badaniem w diagnostyce *pheochromocytoma*. U pacjentów z zespołem mnogich nowotworów endokrynych (MEN) i u członków ich rodzin oznaczanie stężenia CgA może służyć ich monitorowaniu, aby jak najwcześniej wykryć pojawienie się w toku obserwacji guza neuroendokrynego trzustki, rakowiaka albo *pheochromocytoma*.

INTRODUCTION

Chromogranin A (CgA) is present in some endocrine cells of adrenals, pituitary, pancreas, thyroid and in cells of diffuse endocrine system (DES) of gastrointestinal and respiratory system. It is co-secreted and co-released together with some amines and peptides, that are present in the neurosecretory granules. In functionally active, and non-active neuroendocrine tumors (NETs) blood CgA level is often elevated, therefore, it is accepted as a main nonspecific marker of NETs (1, 2).

CHROMOGRANIN A: STRUCTURE AND BIOLOGICAL FUNCTION

Chromogranin A is an acidic protein with a molecular weight of 48 kDa that is composed of 439 amino acids (3). The human CgA gene (CHGA) is located on chromosome 14 (4). There are 10 dibasic sites in human CgA, which are potential sites for proteolytic cleavage (5). CgA occurs in two main conformations: random coil (60-65%) and alpha-helix (25-40%). Alteration of CgA conformation is pH and calcium ions dependent (6, 7). CgA is a protein binding Ca^{2+} ions.

Many regions of CgA are homologous with Ca²⁺ binding protein – calmodulin (8). CgA is a member of the chromogranin family. The granin family consists of eight proteins including: CgA, chromogranin B (CgB), secretogranin II, secretogranin III, secretogranin IV, secretogranin V, secretogranin VI, VGF (9). Posttranslational processing of CgA molecule leads to the formation of smaller biologically active peptides, such as: vasostatin I, vasostatin II, chromacin, pancreastatin, WE-14, parastatin, catestin (10). These CgA-derived peptides due to their influence on the secretion of other hormone, play an indirect role in the metabolism of lipids, carbohydrates, calcium homeostasis, catecholamine secretion, and possess some activities on the cardiovascular system (e.g. vasoconstriction, vasodilatation). They participate also in regulation of secretion of some hormones (e.g. insulin, glucagon, leptin, LH, FSH, PTH), and play some role in the defense mechanism of the respiratory system (antimicrobial activity against bacteria, fungi) (11-15).

PRE-ANALYTICAL AND ANALYTICAL ASPECTS OF CHROMOGRANIN A (CgA) MEASUREMENT IN BLOOD

Measurement of blood CgA concentration appeared possible despite the presence in blood of circulating CgA fragments induced by proteolysis (16).

The first radioimmunoassay for measurements of chromogranin A was introduced by O'Connor and Bernstein in 1984 (17). The next generation assays were based on sandwich methods with the use of monoclonal or polyclonal antibodies (18). Currently few commercial assays are available: IRMA (CgA-RIA CT, CIS Bio International-Schering, Gif-sur-Yvette, France), DAKO chromogranin A ELISA kit (DAKO A/S, Glos-

trup, Denmark), RIA (EuroDiagnostica, Malmo, Sweden), TRACE (Kryptor System; B-R-A-H-M-S GmbH, Thermo Scientific, Germany). These assays differ in test structure, use different antibodies and differently calibrated standards. The applied in these assay monoclonal or polyclonal antibodies recognize different epitopes of CgA molecule and bind also some CgA fragments (19-21). Main characteristics of the mentioned method for determination of CgA are presented in table 1.

Lack of the recognized international standard for CgA, differences of methodology and specificity of the antibodies used, cause that individual CgA measurements performed with different CgA assays cannot be directly compared (22-23).

Using two commercial assays (IRMA and ELISA), we were able to show that CgA concentration is markedly higher in plasma (EDTA, heparin) than in serum (difference 12-70%), therefore different reference ranges should be applied for serum and for plasma samples. Our finding may be explained by the known fact that CgA can partially aggregate at high concentration of free Ca²⁺ ions. In plasma samples (EDTA) anticoagulation occurs through the binding of Ca²⁺ ions, therefore absence of free Ca²⁺ ions may protect CgA from partial aggregation (24). Apart of the tendency for aggregation CgA is a relatively stable protein, although one recent study has indicated that storage of samples over 24 hrs and 48 hrs at +4°C might decrease CgA concentration by 15% and 44% respectively (25). No significant differences were found between CgA levels in men and women (26, 27). In one study, however, authors noted higher concentrations of CgA in males than females, but in another paper CgA levels were higher in females than men, regardless of age (28, 29). Daily

Table 1. Comparison of the currently available methods for determination of CgA concentration.

Method	Kit producer	Antibody	Standard	Unit	Sort of biological material (according to the kit producer)	Upper reference range (according to the kit producer)
Immunoradiometric (IRMA)	CIS Bio	2 monoclonal	rh CgA	ng/ml	serum plasma	serum 98 ng/ml plasma?
ELISA	CIS Bio	2 monoclonal	rh CgA	ng/ml	serum plasma	serum 98 ng/ml plasma?
ELISA	DAKO	2 polyclonal	23 kDa C-terminal fragment of CgA	U/l	plasma (EDTA, heparin)	serum? plasma 2-18 U/l
Radioimmunoassay (RIA)	EuroDiagnostica	1 polyclonal	CgA fraction purified from urine (patients with carcinoid tumours)	nmol/l	serum plasma (EDTA, heparin)	serum and plasma ≤ 3 nmol/l
ELISA	ALPCO	2 polyclonal	rh CgA	ng/ml	plasma (EDTA)	serum? plasma 100 ng/ml
Automated immunometric assay (Kryptor)	B-R-A-H-M-S	2 monoclonal	rh CgA	µg/l	serum	serum male: 84.7 µg/l female: 43.2 µg/l plasma?

rh CgA – human recombinant CgA

fluctuation of blood CgA concentration can be approximately 20-25%, and higher levels are observed in the late afternoon and at night (30, 31). Moderate exercise may exert a minor effect on CgA concentration (32). The CgA levels may also be influenced by ingestion of a meal, therefore blood for its measurement should be collected on fasting preferably in the morning (33, 34).

There are two groups of drugs which strongly influence CgA concentration: proton pump inhibitors (PPI) and H₂-receptor antagonists (H₂-RA) (35). Long-term use of PPI, and in some cases even a short-term treatment too (1-2 weeks), cause a significant increase of CgA concentration in blood, reaching sometimes levels like those observed in advanced NET tumours with metastases (36, 37). To avoid the effect of PPIs on CgA, if only possible, proton pump inhibitors should be discontinued for two weeks, before blood sampling, or PPI should be temporarily replaced by H₂-RA, and this later drug should be discontinued 3 days before blood collection (38, 39). Treatment with corticosteroids may increase the concentration of CgA about 2-fold. The hypotensive drugs, have a little or no effect on CgA concentration (40, 41). During chemotherapy CgA levels may increase temporarily due to the tissue damage and/or nephrotoxic effect of such drugs (42, 43). The list of drugs and pathological conditions which can have influence on CgA concentration is presented in the table (tab. 2).

Table 2. Drugs and pathological conditions which can have influence on the CgA blood level.

High or moderate increase of the blood CgA level	Moderate or little increase of the blood CgA level
<ul style="list-style-type: none"> - proton-pump inhibitors - histamine H₂ receptor-blockers - chronic atrophic gastritis - impaired renal function - prostate cancer and BPH 	<ul style="list-style-type: none"> - inflammatory bowel disease - untreated essential hypertension - acute coronary syndrome - cardiac insufficiency - impaired liver function - hepatocellular carcinoma - pancreatic adenocarcinoma - hyperthyroidism - hyperparathyroidism - rheumatoid arthritis (RF IgM) - Parkinson disease - pregnancy

Practical recommendations for monitoring the concentration of CgA are presented in table 3.

Table 3. Practical recommendations for monitoring the concentration of CgA.

<ul style="list-style-type: none"> - The same method, preferably in the same laboratory - Use the same type of biological material (serum, EDTA-plasma, heparin-plasma) - Results refer to the reference range established for serum or plasma - Order blood collection preferably in the morning on fast (> 8 hr after last meal) - Withdraw drugs (proton pump inhibitors for 2 weeks, H₂-receptor blockers for 3 days) - Consider other non-specific factors which can have influence on CgA blood level

CHROMOGRANIN A – NEUROENDOCRINE TUMOURS MARKER

Neuroendocrine tumours are considered as rare, heterogeneous neoplasms. Some of these tumours secrete into the blood various substances, such as: hormones, pre-hormones, amines, various peptides which measurements have been applied for diagnostic purposes, assessment of treatment efficacy, and disease prognosis.

CgA is a main nonspecific neuroendocrine tumour marker. Elevated blood CgA level can be usually detected in: gastroenteropancreatic neuroendocrine tumours (GEP-NET), pheochromocytomas, neuroblastomas, MEN syndromes, bronchopulmonary NETs, medullary thyroid carcinoma, small-cell lung carcinoma, and some other very rare NETs (44). Dimension of CgA level elevation depends of the cell type, number of secretory granules, tumour volume, localization and stage of the disease (metastases) (45).

GEP-NET

CgA measurement became a routine investigation in the diagnosis of GEP-NET (46), but is especially helpful in monitoring the effects of treatment. In small NETs, however (e.g. insulinoma) CgA level may not be elevated (47), therefore in general the sensitivity of CgA in GEP-NET is 10-100%, and specificity 68-100%. In patient with metastasis, the sensitivity is 60-100%. In some cases CgA level can increase by 100-1000 times above the cut-off value (the highest values are observed in carcinoids with liver metastases). CgA is considered as an independent prognostic factor of survival in patients with midgut GEP-NET (48). The highest sensitivity (80-100%) of CgA is observed in: gastrinoma, carcinoid tumour, and glucagonoma. Concentration of circulating CgA is associated with the degree of differentiation of neuroendocrine tumors (in poorly differentiated tumours CgA level are lower than in the highly differentiated tumors). According to the established recommendation in poorly differentiated tumours, CgA level should be measured every 2-3 months, whereas in other cases, at 6-12 months intervals (49).

PHEOCHROMOCYTOMA AND OTHER ADRENAL TUMOURS

CgA is secreted by the neuroendocrine cells of adrenal medulla. CgA levels correlate with tumour mass and secretion of catecholamines, but this correlation disappears in large tumours (50). The sensitivity of CgA is 80-96% (51, 52). CgA can be considered as a complementary investigation in the diagnostic procedure of pheochromocytoma (together with catecholamines the sensitivity is approx. 100%). In preliminary differential diagnosis of adrenal tumours a markedly increased CgA level might be a useful additional marker of pheochromocytoma, however there are some cases of "silent" pheochromocytoma in which CgA level is not elevated.

ed. On the other side we should know that there are some cases of hormonally active adenomas and adrenal carcinomas secreting cortisol in which blood CgA levels may be moderately increased (53).

It is important to note that pheochromocytoma should be excluded before any invasive diagnostic or therapeutic procedure is undertaken to avoid the development of catecholaminergic crisis. It has been reported that in clinically silent cases of pheochromocytoma, after administration of glucocorticoids in a dose exceeding 1 mg of dexamethasone, there is a potential threat of severe hypertensive crisis, with life-threatening symptoms (low dose DST – 1 mg orally – has not been associated with such crisis) (54). Therefore, special care is necessary while planning the performance of high dose dexamethasone suppression tests in insufficiently diagnosed patients with adrenal tumour. Similar caution is advised when prescribing glucocorticoids as a pre-treatment before CT or MRI in patients allergic to contrast dye. For the above reasons, an additional test helping to confirm or exclude pheochromocytoma in patients with an asymptomatic adrenal tumour seems warranted.

MEN SYNDROMES

In patients with multiple endocrine neoplasia (MEN) investigation of CgA level may be used for monitoring eventual coexistence or appearance with time of carcinoid, pancreatic neuroendocrine tumours or pheochromocytoma (55). Sensitivity of CgA in patients with MEN-1 is approximately 60% (56).

DETERMINATION OF THE BLOOD CgA CONCENTRATION IN SOME OTHER DISEASES

During long-term gastric acid inhibition serum CgA levels correlate with serum gastrin and reflect the presence and severity of fundic enterochromaffin (ECL) cells proliferative changes. Therefore it is proposed that monitoring blood CgA levels might be a useful screening test for ECL cell hyperplasia. It is suggested, that in cases with markedly increased CgA values an indication for endoscopic and histological examination of the gastric mucosa should be considered (57). CgA level may increase slightly also in patients with liver cirrhosis, chronic hepatitis, pancreatitis, inflammatory bowel diseases, obstructive pulmonary disease, sepsis, and in extreme physical stress (58).

BIBLIOGRAPHY

- Lamberts SWJ, Hofland LJ, Nobels FRE: Neuroendocrine tumor markers. *Front Neuroendocrinol* 2001; 22: 309-339.
- O'Connor DT, Deftos LJ: Secretion of chromogranin A by peptide-producing endocrine neoplasms. *N Engl J Med* 1986; 314: 1145-1151.
- Inomoto C, Osamura RY: Formation of secretory granules by chromogranins. *Med Mol Morphol* 2009; 42: 201-203.
- Wu HJ, Rozansky DJ, Parmer RJ et al.: Structure and function of the chromogranin A gene. *J Biol Chem* 1991; 266: 13130-13134.
- Bartolomucci A, Possenti R, Mahata SK et al.: The extended Granin Family: structure, function, and biomedical implications. *Endocr Rev* 2011; 32: 755-797.
- Yoo SH, Albanesi JP: Ca²⁺-induced conformational change and aggregation of chromogranin A. *J Biol Chem* 1990; 265: 14414-14421.
- Malecha A, Donica H: Chromogranina A – budowa, właściwości, funkcje i znaczenie diagnostyczne w guzach neuroendokrynych przewodu pokarmowego (GEP-NET). *Diag Lab* 2008; 44: 347-361.
- Montero-Hadjadje M, Elias S, Chevalier L et al.: Chromogranin A promotes peptide hormone sorting to mobile granules in constitutively and regulated secreting cells: role of conserved N- and C-terminal peptides. *J Biol Chem* 2009; 284: 12420-12431.
- Taupenot L, Harper KL, O'Connor DT: The chromogranin/secretogranin family. *N Engl J Med* 2003; 348: 1134-1149.
- Modlin IM, Gustafsson BI, Moss SF et al.: Chromogranin A – biological function and clinical utility in neuroendocrine tumor disease. *Ann Surg Oncol* 2010; 17: 2427-2443.
- Di Comite G, Morganti A: Chromogranin A: a novel factor acting at the cross road between the neuroendocrine and the cardiovascular system. *J Hypertens* 2011; 29: 409-414.
- Mahapatra NR, Taupenot L, Courel M et al.: The trans-Golgi proteins SCLIP and SCG10 interact with chromogranin A to regulate neuroendocrine secretion. *Biochemistry* 2008; 47: 7167-7178.
- Schmid GM, Meda P, Caille D et al.: Inhibition of insulin secretion by betagranin, an N-terminal chromogranin A fragment. *J Biol Chem* 2007; 282: 12717-12724.
- Helle KB: The granin family of uniquely acidic proteins of the diffuse neuroendocrine system: comparative and functional aspects. *Biol Rev Camb Philos Soc* 2004; 79: 769-794.
- Dieplinger B, Gegenhuber A, Struck J et al.: Chromogranin A and C-terminal endothelin-1 precursor fragment add independent prognostic information to amino-terminal proBNP in patients with acute destabilized heart failure. *Clin Chim Acta* 2009; 400: 91-96.
- Rosa P, Gerdes HH: The granin family: markers for neuroendocrine cells and tools for the diagnosis of neuroendocrine tumors. *J Endocrinol Invest* 1994; 17: 207-225.
- O'Connor DT, Bernstein KN: Radioimmunoassay of chromogranin A in plasma as a measure of exocytotic sympathoadrenal activity in normal subjects and patients with pheochromocytoma. *N Engl J Med* 1984; 311: 764-770.
- Bernini GP, Moretti A, Ferdeghini M et al.: A new human chromogranin A immunoradiometric assay for the diagnosis of neuroendocrine tumours. *Br J Cancer* 2001; 84: 636-642.
- Lawence B, Gustafsson BI, Kidd M et al.: The clinical relevance of chromogranin A as a biomarker of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin N Am* 2011; 40: 111-134.
- Molina R, Alvarez E, Aniel-Quinoga A et al.: Evaluation of chromogranin A determined by three different procedures in patients with benign diseases, neuroendocrine tumors and other malignancies. *Tumour Biol* 2011; 32: 13-22.
- Popovici T, Moreira B, Schlaqeter MH et al.: Automated two-site immunofluorescent assay for the measurement of serum chromogranin A. *Clin Biochem* 2014; 47: 87-91.
- O'Toole D, Grossman A, Gross D et al.: ENETS Consensus Guidelines for the standards of care in neuroendocrine tumors: biochemical markers. *Neuroendocrinology* 2009; 90: 194-202.
- Stridsberg WG, Eriksson B, Öberg K et al.: A comparison between three commercial kits for chromogranin A measurements. *J Endocrinol* 2003; 177: 337-341.
- Glinicki P, Kapuścińska R, Jeske W: The differences in chromogranin A (CgA) concentration measured in serum and in plasma by IRMA and ELISA methods. *Endokrynol Pol* 2010; 61: 346-350.
- Pedersen L, Nybo M: Preanalytical factors of importance for measurement of chromogranin A. *Clin Chim Acta* 2014. doi: 10.1016/j.cca.2014.04.026.
- Dittadi R, Meo S, Gion M et al.: Biological variation of plasma chromogranin A. *Clin Chem Lab Med* 2004; 42: 109-110.
- Drivsholm L, Paloheimo LI, Österlind K: Chromogranin A: a significant prognostic factor in small cell lung cancer. *Br J Cancer* 1999; 81: 667-671.
- Tsao KC, Wu JT: Development of an ELISA for the detection of serum chromogranin A (CgA) in prostate and non-neuroendocrine carcinomas. *Clin Chim Acta* 2001; 313: 21-29.
- Braga F, Ferraro S, Mozzi R et al.: Biological variation of neuroendocrine tumor markers chromogranin A and neuron-specific enolase. *Clin Biochem* 2013; 46: 148-151.
- Takiyuddin MA, Neumann HP, Cervenka JH et al.: Ultradian variations of chromogranin A in human. *Am J Physiol* 1991; 261: 939-944.
- Gianpaolo B, Angelica M, Antonio S: Chromogranin A in normal subjects, essential hypertensives and adrenalectomized patients. *Clin Endocrinol* 2002; 57: 41-50.

32. Elias An, Wilson AF, Pandian MR et al.: Chromogranin A concentrations in plasma of physically active men after acute exercise. *Clin Chem* 1992; 38: 2348-2349.
33. Sanduleanu S, De Bruine A, Stridsberg M et al.: Serum chromogranin A as a screening test for gastric enterochromaffin-like cell hyperplasia during acid – suppressive therapy. *Eur J Clin Invest* 2001; 31: 802-811.
34. Glinicki P, Kuczerowski R, Jeske W: The effect of meal on the serum concentration of chromogranin A (CgA) – a preliminary report. *Diag Lab* 2011; 47: 165-168.
35. Pregon I, Herszényi L, Juhász M et al.: Effect of proton-pump inhibitor therapy on serum chromogranin A level. *Digestion* 2011; 84: 22-28.
36. Kuipers EJ: Proton pump inhibitors and gastric neoplasia. *Gut* 2006; 55: 1217-1221.
37. Mosli HH, Dennis A, Kocha W et al.: Effect of short-term proton pump inhibitor treatment and its discontinuation on chromogranin A in healthy subjects. *J Clin Endocrinol Metab* 2012; 97: 1731-1735.
38. Waldum HL, Arnestad JS, Brenna E et al.: Marked increase in gastric acid secretory capacity after omeprazole treatment. *Gut* 1996; 39: 649-653.
39. Syversen U, Ramstad H, Gamme K et al.: Clinical significance of elevated serum chromogranin A levels. *Scand J Gastroenterol* 2004; 10: 969-973.
40. Nobels FRE, Kweekkeboom DJ, Bouillon R et al.: Chromogranin A: its clinical value as marker of neuroendocrine tumors. *Eur J Clin Invest* 1998; 28: 431-440.
41. Fischer-Colbrie R, Wohlfarter T, Schmid KW et al.: Dexametasone induces an increased biosynthesis of chromogranin A in rat pituitary gland. *J Endocrinol* 1989; 121: 487-494.
42. Lamberts SW, Hofland LJ, Nobels FRE: Neuroendocrine tumor markers. *Front Neuroendocrinol* 2001; 22: 309-339.
43. Spadaro A, Ajello A, Morace C et al.: Serum chromogranin-A in hepatocellular carcinoma: diagnostic utility and limits. *World J Gastroenterol* 2005; 11: 1987-1990.
44. Stivanello M, Berruti A, Torta M et al.: Circulating chromogranin A in the assessment of patients with neuroendocrine tumours. A single institution experience. *Ann Oncol* 2001; 12 (suppl. 2): 73-77.
45. Feldman SA, Eiden LE: The chromogranins: Their roles in secretion from neuroendocrine cells and as markers for neuroendocrine neoplasia. *Endocrine Pathology* 2003; 14: 3-23.
46. Zatelli MC, Torta M, Leon A et al.: Chromogranin A as a marker of neuroendocrine neoplasia: an Italian Multicenter Study. *Endocrine-Related Cancer* 2007; 14: 473-482.
47. Nobels FRE, Kweekkeboom DJ, Coopmans W et al.: Chromogranin A as serum marker for neuroendocrine neoplasia: comparison with neuron-specific enolase and the α -subunit of glycoprotein hormones. *J Clin Endocrinol Metab* 1997; 82: 2622-2628.
48. Arnold F, Wilke A, Rinke A et al.: Plasma chromogranin A as a marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. *Clin Gastroenterol Hepatol* 2008; 6: 820-827.
49. Kos-Kudła B, Ćwikła J, Jarząb B et al.: Polish diagnostic and therapeutic guidelines in gastroenteropancreatic neuroendocrine tumour (GEP-NET). *Endokrynol Pol* 2006; 57: 267-272.
50. Stolk RF, Bakx C, Mulde J et al.: Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines? *J Clin Endocrinol Metab* 2013; 98: 1100-1106.
51. Giovannella L, Ceriani L, Balerna M et al.: Diagnostic value of serum chromogranin A combined with MIBG scintigraphy in patients with adrenal incidentalomas. *Q J Nucl Med Mol Imaging* 2008; 52: 84-88.
52. Bilek R, Šafařík K, Ciprova V et al.: Chromogranin A, a member of neuroendocrine secretory proteins as a selective markers for laboratory diagnosis of Pheochromocytoma. *Physiol Res* 2008; 57 (suppl. 1): 171-179.
53. Glinicki P, Jeske W, Bednarek-Papierska L et al.: Chromogranin A (CgA) in adrenal tumours. *Endokrynol Pol* 2013; 64: 358-362.
54. Rosas AL, Kasperlik-Zaluska AA, Papierska L et al.: Pheochromocytoma crisis induced by glucocorticoids: a report of four cases and review of literature. *Eur J Endocrinol* 2008; 158: 423-429.
55. Abou-Saif A, Gibril F, Ojeaburu JV et al.: Prospective study of the ability of serial measurements of serum chromogranin A and gastrin to detect changes in tumor burden in patients with gastrinomas. *Cancer* 2003; 98: 249-261.
56. Öberg K, Skogseid B: The ultimate biochemical diagnosis of endocrine pancreatic tumours in MEN-1. *J Intern Med* 1998; 243: 471-476.
57. Sanduleanu S, De Bruine A, Stridsberg M et al.: Serum chromogranin A as a screening test for gastric enterochromaffin-like cell hyperplasia during acid-suppressive therapy. *Eur J Clin Invest* 2001; 31: 802-811.
58. Trapé J, Filella X, Alsina-Donadeu M et al.: Increased plasma concentrations of tumour markers in the absence of neoplasia. *Clin Chem Lab Med* 2011; 49: 1605-1620.

received/otrzymano: 15.10.2014
 accepted/zaakceptowano: 07.11.2014