Chromogranin A Assay and ^{131}I-MIBG Scintigraphy for Diagnosis and Follow-Up of Pheochromocytoma

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We assessed the performance of a new serum chromogranin A (CgA) assay in combination with the results of ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy for diagnosis and follow-up in 89 patients with clinical findings suggestive of pheochromocytoma. **Methods:** The study population consisted of 41 patients with proven pheochromocytoma and 48 patients with refuted pheochromocytoma. Eighty-seven scintigraphy examinations were performed, 52 in patients with proven pheochromocytoma (39 before surgery and 13 after surgery) and 35 in patients with refuted pheochromocytoma. **Results:** The sensitivity of the CgA level was 90.2%, and the specificity was 99.0% and 92.3% in the control and refuted pheochromocytoma groups, respectively. A significant relationship was seen between serum levels of CgA and tumor mass ($r = 0.70$; $P < 10^{-5}$). The postoperative CgA level was an early and accurate predictor of curative surgery or relapse. The concordance between CgA levels and scintigraphic data was 90.8%. **Conclusion:** Serum CgA level is an effective marker of pheochromocytoma. Increased levels strongly correlate with tumor mass; therefore, small tumors may go undetected. The concordance between CgA level and the results of ^{131}I-MIBG scintigraphy is high. A CgA level in the reference range is highly predictive of normal scintigraphy findings.

Key Words: pheochromocytoma; ^{131}I-metaiodobenzylguanidine scan; chromogranin A assay

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Chromogranin A (CgA) was discovered in the catecholamine-containing chromaffin granules of the adrenal medulla (*1*). CgA belongs to a unique family of secretory chromogranin and secretogranin proteins. This acidic, soluble protein is present in the secretory vesicles throughout the neuroendocrine system, from which it is cosecreted with a wide variety of peptide hormones and neurotransmitters such as dopamine, norepinephrine, and epinephrine (*2*,*3*). The gene that encodes for CgA is on chromosome 14 (*4*–*6*). The unique expression of CgA in neuroendocrine cells depends on a complex mechanism of transcriptional regulation (*7*–*9*). CgA plays several biologic roles, both within the secretory granules and after release from neuroendocrine cells (*10*,*11*). A novel fragment of CgA, known as catestatin (CgA 344–364), inhibits catecholamine release from chromaffin cells and may therefore constitute an endogenous autocrine feedback regulator of sympathoadrenal activity (*12*–*14*).

CgA can be used as an immunohistochemical marker and as a sensitive and specific serum marker of neuroendocrine tumors (*15*–*20*). Only some studies from a few teams have shown high levels of CgA in patients with pheochromocytoma and the relationship between these levels and the usual biochemical markers (*21*–*29*). Nevertheless, the role of CgA in comparison with that of ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy has not been clearly defined, nor has the role of CgA in follow-up after surgical excision of the tumor been studied.

In a prospective 2-y study, we investigated the serum levels of CgA in a large group of patients with suspected pheochromocytoma and compared the findings with those of MIBG scintigraphy and other biochemical tests. We specifically tried to determine the role of CgA compared with that of other biologic markers, both for diagnosis and for distinguishing tumor recurrence and cure.

MATERIALS AND METHODS

Subjects

Serum samples were obtained from 89 patients (47 women, 42 men) referred because of clinical findings suggestive of pheochromocytoma. These patients were classified into 2 groups.

The first group, group A, consisted of 41 patients (20 women, 21 men) with a histologically confirmed diagnosis of pheochromocytoma. Thirty-two patients had a unilateral adrenal pheochromocytoma (28 sporadic, 1 familial, 2 Hippel–Lindau, and 1 type 2A multiple endocrine neoplasia [MEN 2A]), 3 patients had a bilateral adrenal pheochromocytoma (1 sporadic, 1 familial, and 1 MEN 2A), and 6 patients had an extra-adrenal pheochromocytoma (paraganglioma) (4 abdominal [3 sporadic and 1 familial], 1 thoracic and sporadic, and 1 cervical and sporadic). The tumors were measured and weighed in the operating room. Two of the pheochromocytomas were proven malignant: one at diagnosis, the other

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during follow-up. Thirty-two patients were reexamined after surgery.

The second group, group B, consisted of 48 patients (27 women, 21 men) with hypertension and either an adrenal mass or increased urinary catecholamines or metanephrines. Pheochromocytoma was classified as refuted in these patients, and this classification was sustained 1 y later. All but 1 of these patients had normal renal function.

A control group, group C, comprised serum samples from 98 healthy blood donors (49 women, 49 men).

Immunoassays

CgA was measured in serum samples stored at −80°C. We used an immunoradiometric assay (CGA-RIA-CT; Cis Bio International, Gif-sur-Yvette, France) with 2 well-characterized monoclonal antibodies: 1 coated on the reaction tube and another labeled with ^{125}I. Human recombinant CgA was used for the standard curve. Bound and free CgA were separated using aspiration.

The within-assay coefficients of variation were <5%. The between-assay coefficients of variation were 9.35% and 7.25% for mean levels of 100 and 370 ng/mL (n = 21), respectively. The sensitivity of detection was 1.5 ng/mL (when the ratio of bound activity to total activity of the standard curve was 0.63%). CgA immunoreactivity remained stable.

The catecholamines and their metabolites (normetanephrine and metanephrine) in urine were measured by high-performance liquid chromatography after extraction and purification.

^{131}I-MIBG Scintigraphy

For the ^{131}I-MIBG study, thyroid uptake of iodine was blocked with prior administration of potassium iodide (130-mg capsule containing 100 mg iodine, given orally once per day for 5 d, starting the day before ^{131}I administration). ^{131}I-MIBG scintigraphy was performed at 24 h and at 48 or 72 h after intravenous injection of 37 MBq (1 mCi) ^{131}I-MIBG. If required, the kidneys or liver were imaged using ^{99m}Tc-diethylenetriaminepentaacetic acid or ^{99m}Tc-sulfur colloid, respectively. In group A, 52 scintigraphy examinations were performed: 39 before surgery and 13 after. In group B, scintigraphy was performed on 35 patients.

Statistical Analysis

The different markers were compared using Spearman rank correlation and receiver operating characteristic (ROC) curve analysis. The area under the curve, considered the single best quantitative index of ROC curves, was determined using a computer program (Metz; University of Chicago, Chicago, IL). The different groups were compared using Kruskal-Wallis ANOVA and the median test of Mann-Whitney. Sensitivity, specificity, and positive and negative predictive values for the CgA test were calculated using the standard formulas.

RESULTS

The results of the CgA determinations (Fig. 1) are summarized in Table 1 (Kruskal-Wallis ANOVA and median test of Mann-Whitney). For groups A and C, ROC curve analysis found that the best upper cutoff level for both sexes was 100 ng/mL. Sensitivity, specificity, and positive and negative predictive values were calculated for groups A and C and for groups A and B and are reported in Table 2 for cutoff levels of 100 and 110 ng/mL.

TABLE 1
CgA Levels in Different Groups

Group	n	CgA level (ng/mL) Mean	SD	Range	P*
Pheochromocytoma	41	632	853	39–3,840	0.001
Refuted pheochromocytoma	39	54.5	30	22–162	NS
Control	98	50.7	12.3	33–105	—

*Comparison with control group.
NS = not statistically significant.

In group A, an increased serum level of CgA was shown in 37 (90.2%) of 41 patients. The 4 patients with CgA levels in the reference range included the 3 patients with the smallest pheochromocytomas (range, 9–14 g) and 1 patient with a cervical paraganglioma (20 g). Two patients had MEN 2A. In both, an asymptomatic pheochromocytoma was found before surgery of the medullary thyroid carcinoma. Five of the 6 paragangliomas had elevated CgA levels.

Relationships with Other Markers

Figure 2 compares the results of the CgA assay with the results of the urinary normetanephrine and metanephrine assays in groups A and B. In group A, a significant relationship was seen between serum levels of CgA and urinary levels of metanephrines with a linear model (r = 0.80; $P < 10^{-4}$) and between serum levels of CgA and urinary levels of catecholamines with a multiplicative model (r = 0.58; P = 0.001) (Spearman rank correlation). The areas under the ROC curves were 0.992 for metanephrines, 0.931 for CgA, and 0.926 for catecholamines, but these values were not significantly different.

Relationship with Tumor Mass

A statistically significant relationship was seen between tumor mass and CgA levels (r = 0.70; $P < 10^{-5}$) and

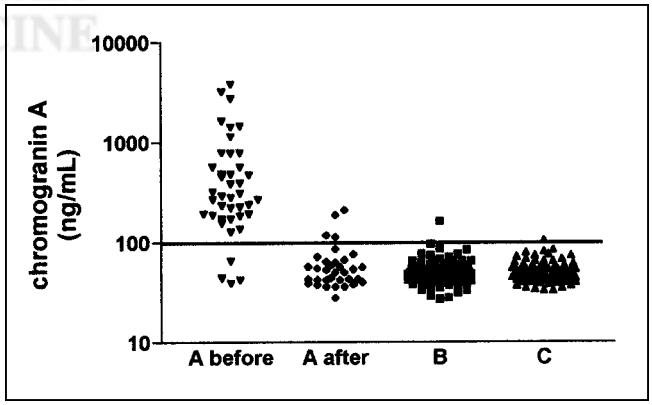

FIGURE 1. Distribution of CgA levels in pheochromocytoma group (A) before surgery and after surgery, in refuted pheochromocytoma group (B), and in control group (C).

TABLE 2
Index Values for Different Cutoff Levels of CgA

Group	Cutoff CgA level (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pheochromocytoma vs. control	100	90.2	99.0	97.3	96.1
	110	90.2	100.0	100.0	96.1
Pheochromocytoma vs. refuted pheochromocytoma	100	90.2	92.3	92.5	90.0
	110	90.2	94.9	94.7	90.3

PPV = positive predictive value; NPV = negative predictive value.

between tumor mass and metanephrine excretion ($r = 0.76$; $P < 10^{-5}$) (Spearman rank correlation).

CgA Level as Postoperative Marker

Of the 32 CgA postsurgical assays, 28 were in the reference range (Fig. 1). The CgA levels were higher than the cutoff level in 4 patients (113, 118, 187, and 399 ng/mL). One of these patients had moderate renal failure without evidence of recurrence, and 2 others had persistent malignant pheochromocytoma. In the fourth, pheochromocytoma was still refuted 1 y later.

CgA Level and ^{131}I-MIBG Scintigraphy

For all patients, the concordance between CgA levels and scintigraphy results was 90.8%. The results are reported in Table 3; 32 patients had positive scan findings and elevated CgA levels, and 47 had negative scan findings and CgA levels in the reference range.

Among the 39 scintigraphy examinations performed on group A before surgery, we noted 34 (87.2%) with positive findings. For 2 of the 3 patients with bilateral pheochromocytoma, scanning showed positive findings in only 1 location. For patients with proven paragangliomas, 5 scans were obtained, and 3 had positive results. Five scans had negative findings: 2 paragangliomas (1 cervical and 1 abdominal) and 3 pheochromocytomas (1 in the patient with MEN 2A and bilateral pheochromocytoma). The 13 scans obtained after surgery had negative findings, as did the 35 group B scans.

Eight discrepancies were observed. In 2 patients, the findings were positive for MIBG but false-negative for CgA. In 6 patients, the findings were negative for MIBG (false-negative in 4 patients with proven pheochromocytoma [3 presurgical, 1 postsurgical and malignant]) but positive for CgA (false-positive in 2 hypertensive patients).

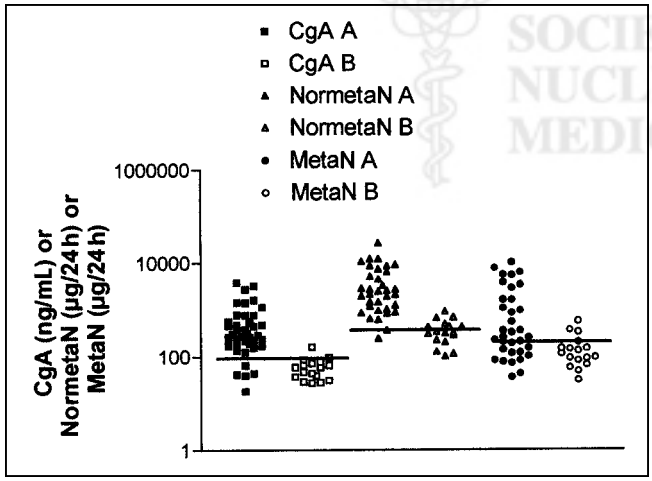

FIGURE 2. Distribution of CgA levels, of normetanephrine urinary levels (NormetaN), and of metanephrine urinary metabolites (MetaN) in pheochromocytoma group (A; $n = 41$) and in refuted pheochromocytoma group (B; $n = 17$).

DISCUSSION

Serum CgA has been advocated as a specific marker in the differential diagnosis of suspected pheochromocytoma. Because CgA is cosecreted with catecholamines, CgA has been suggested as an alternative to catecholamine testing in the diagnosis of pheochromocytoma.

The sensitivity (90.2%) found in our study agrees with sensitivities found in previous studies: 89% for Nobels et al. (*17*), 83% for Hsiao et al. (*22*,*23*), and 86% for Canale and Bravo (*30*). Relatively little overlap occurred in CgA values between pheochromocytoma patients and patients with hypertension (*31*). In our assay, the overlap was approximately 20%. If the CgA cutoff level is raised to 110 ng/mL, the specificity in our study increases to 94.9%, with the same sensitivity.

TABLE 3
Concordance Between MIBG Scintigraphy Results and CgA Level

Group	MIBG+/ CgA+	MIBG+/ CgA−	MIBG−/ CgA+	MIBG−/ CgA−
Pheochromocytoma				
Before surgery	32	2	3	2
After surgery	0	0	2	11
Refuted pheochromocytoma	0	0	1	34

+ = positive; − = negative.

Elevated levels were found in 5 of 6 patients with paraganglioma (extra-adrenal pheochromocytoma). These results differ from those of previous studies (*17*,*22*,*23*,*26*,*28*,*29*), in which CgA levels in patients with paraganglioma were within the reference range. Paragangliomas may be small tumors such as insulinomas or pituitary adenomas and are usually detected at an early stage because they rapidly induce symptoms. Paragangliomas may differ from pheochromocytomas in presentation, clinical course, and biochemical pattern. However, at the time of diagnosis, problems may be the same for the paragangliomas as for the pheochromocytomas.

Another difference from previous studies lies in the antibodies used in the assays. Several recently developed immunoassays showed a variable degree of cross-reaction with the cleavage products of CgA present in the circulation. CgA is highly affected by C terminal proteolysis (*11*,*32*,*33*). The discrepancies between our findings and those of previous studies may be caused by the characteristics of our assay. Most studies have used radioimmunoassays with polyclonal antibodies partly directed toward the C terminal portion of the CgA molecule. Our assay is based on recognition of the middle domain, which is less subject to proteolysis (*33*). Jensen et al. (*34*) showed that the level of CgA in different tissues varied with the assay used. Hence, in a carcinoid tumor, for instance, the level varied from 0.5 to 34 nmol/g tissue depending on the specificity of the CgA assay. In all tumors, the lowest levels were measured with the assay specific for the NH_2 terminus of CgA. Only some CgA assays appear useful for diagnosis of neuroendocrine tumors (*33*,*34*).

We showed a significant positive correlation between serum CgA levels, urinary metanephrine levels, and the mass of the pheochromocytoma tumor. The smallest extracted masses corresponded to CgA levels in the reference range (2 patients with asymptomatic pheochromocytomas in MEN 2A). In MEN 2A, approximately 40% of carriers have pheochromocytoma. Selecting a cutoff level is not easy. In the study of Neumann et al. (*25*), the sensitivity of CgA for detection of pheochromocytoma was only 52% for patients with familial disorders. The increase in serum CgA level occurs relatively late in the evolution of these tumors.

Postoperative CgA determination may be useful as a marker of recurrence (*35*). In this study, postoperative CgA levels fell to within normal limits in 28 of 32 patients. Four CgA levels remained elevated. For 1 patient, the follow-up was too short for conclusions to be drawn; 2 other patients presented with a persistent malignant pheochromocytoma; the disease of the fourth patient was cured, but he had moderate renal failure. Various studies indicate that serum CgA levels are elevated in uremic patients. Such elevations are related to the retention of CgA granules and are proportional to the degree of uremia (*30*,*36*,*37*).

MIBG scintigraphy has proven highly specific as a tool for detection of pheochromocytoma but lacks sensitivity. Roelants et al. (*38*) published a revised interpretation. In our study, the results of MIBG scans were positive in 60% of paraganglioma patients and 86.6% of pheochromocytoma patients, in agreement with the findings of Jalil et al. (*39*). These authors found an 88% sensitivity for adrenal localization and a 64% sensitivity for extra-adrenal localization, whereas Manelli et al. (*40*) found a sensitivity of 88.5%. The concordance between CgA levels and MIBG scintigraphy results is fair (90.8%). Of 53 scans with negative findings, 47 had CgA levels in the reference range. In the 13 postoperative studies, the normality of the CgA levels was predictive of the normality of the MIBG scintigraphy findings.

Because the ROC areas under the curves for CgA did not significantly differ from those for normetanephrine, metanephrine, or catecholamines, CgA determination should be preferred to high-performance liquid chromatography studies as being easier and cheaper. Incorporating CgA determination early in the work-up of patients with suspected pheochromocytoma should be cost-effective in terms of both money and radiation dose to the patients.

CONCLUSION

Our monoclonal antibody assay, which recognizes the middle domain, is highly specific for adrenal pheochromocytoma or paraganglioma in patients without renal dysfunction. In the diagnosis and follow-up of pheochromocytoma, the serum CgA assay should be used as an alternative to urinary catecholamine measurement. The CgA assay is poorly influenced by drugs commonly used in the treatment of pheochromocytoma. CgA levels are parallel to those of the tumor mass; thus, the smallest masses can go undetected. Postoperative CgA levels are a good index of the curative outcome of surgery. If in the reference range, CgA level predicts the normality of MIBG scintigraphy findings. Considering costs, irradiation, and availability, one should determine the serum CgA level before performing MIBG scintigraphy for localization of pheochromocytoma.

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