

## Prevalence of Chromogranin A in Chronic Dyspepsia, IBS and Chronic Diarrhea at Maharat Nakhon Ratchasima Hospital

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### Abstract

Many different clinical presentations of Neuroendocrine tumors (NETS) are occasional loose stools, episodic flushing or intermittent abdominal pain which is often misdiagnosed as gastroenteritis, menopause, peptic ulcer disease or irritable bowel disease. **Aim:** To study the prevalence of chromogranin A (CgA) in chronic dyspepsia, IBS and chronic diarrhea at Maharat Nakhon Ratchasima Hospital. **Patients & Method:** All patients (age>15 years) who presented with chronic dyspepsia, IBS and chronic diarrhea at Medical Department of Maharat Nakhon Ratchasima Hospital during February-April 2010 were enrolled. The exclusion criteria were chronic renal failure, previous PPI use within 1 week, chronic heart failure. The blood samples were obtained and plasma CgA level was measured with radioimmunoassay commercially kits in central laboratory of Ramathibodi Hospital, Bangkok, Thailand. **Results:** Seventy-five patients were enrolled. Most of them were female (72%), living in Nakhon Ratchasima Province (94.7%) and had no co-morbid diseases (78.7%). Their mean age was  $49.5 \pm 12.1$  years. Majority of samples (86.7%) presented with chronic dyspepsia and median duration of their symptoms was 1 year. The mean of plasma CgA level was  $246 \pm 10.9$  ng/ml (except 3 cases which had CgA level more than 870 ng/ml). Of them, 39 patients (52%) had plasma CgA level more than the cut off level. In high plasma CgA level (positive) group, plasma CgA test was repeated among 11 cases and 3 of them had persistently high levels (27.3%); >870, 222.3 and 109.9 ng/ml. The esophago-gastroduodenoscopy and colonoscopy were done in 19 and 8 patients and no significant endoscopic finding was found. The clinical follow up of all positive group was performed without evidence of NETs even in 3 cases with persistently positive test. **Conclusion:** The prevalence of positive CgA testing in dyspepsia, IBS and chronic diarrhea at Maharat Nakhon Ratchasima Hospital was high but there was no clinical implementation for early warning of NETs detection.

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**บทคัดย่อ** ความชุกของโคโมกรานินเอนในผู้ป่วยโรคกระเพาะอาหาร โรคไอบีเอส และท้องเสียเรื้อรัง  
ในโรงพยาบาลมหาราชนครราชสีมา  
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ผู้ป่วยมะเร็งนี้มาด้วยอาการที่หลากหลายได้แก่ ถ่ายเหลวบางครั้ง ปวดท้องออกร้อนท้องเป็นพัก ๆ ซึ่งอาจวินิจฉัยผิดเป็นลำไส้อักเสบ ภาวะการขาดฮอร์โมนเพศ โรคกระเพาะอาหารหรือโรคลำไส้แปรปรวนได้ **วัตถุประสงค์:** เพื่อศึกษาความชุกของโคโมกรานินเอนในผู้ป่วยโรคกระเพาะอาหารเรื้อรัง โรคไอบีเอส และท้องเสียเรื้อรังในโรงพยาบาลมหาราชนครราชสีมา **ผู้ป่วยและวิธีการ:** กลุ่มศึกษาได้แก่ ผู้ป่วยอายุมากกว่า 15 ปีทุกรายที่มาด้วยปัญหาปวดท้องเรื้อรัง โรคไอบีเอสหรือท้องเสียเรื้อรังในโรงพยาบาลมหาราชนครราชสีมาระหว่างกุมภาพันธ์ถึงเมษายน พ.ศ.2553 ที่ยินยอมเข้าร่วมการศึกษา กลุ่มที่ถูกคัดออกได้แก่ โรคไตวายเรื้อรัง ได้รับยาลดกรดที่ยับยั้งปั๊มภายใน 1 สัปดาห์และโรคหัวใจวายเรื้อรัง ทำการตรวจเลือดหาระดับสารโคโมกรานินเอนด้วยวิธีเรดิโออิมมูโนที่ห้องปฏิบัติการโรงพยาบาลรามารับดี กรุงเทพมหานคร **ผลการศึกษา:** ผู้ป่วยที่เข้าร่วมการศึกษาทั้งหมด 75 ราย ส่วนใหญ่เป็นเพศหญิง (ร้อยละ 72) อาศัยในจังหวัดนครราชสีมา (ร้อยละ 94.7) ไม่มีโรคร่วม (ร้อยละ 78.7) อายุเฉลี่ย  $49.5 \pm 12.1$  ปี ผู้ป่วยส่วนใหญ่ (ร้อยละ 86.7) มาด้วยปัญหาโรคกระเพาะอาหารเรื้อรัง โดยมีอาการประมาณ 1 ปี ค่าเฉลี่ยระดับโคโมกรานินเอน  $246 \pm 10.9$  นาโนกรัมต่อมิลลิลิตร (ยกเว้น 3 รายที่ระดับสูงมากกว่า 870 นาโนกรัมต่อมิลลิลิตร) โดย 39 ราย (ร้อยละ 52) มีโคโมกรานินเอนสูงผิดปกติ ในกลุ่มที่โคโมกรานินเอนสูงผิดปกติ ได้ตรวจซ้ำ 11 รายแต่ยังคงมีโคโมกรานินเอนสูงผิดปกติเพียง 3 ราย (ร้อยละ 27.3) [ $>870$ , 222.3 และ 109.9 นาโนกรัมต่อมิลลิลิตร] 19 รายได้รับการส่องกล้องตรวจทางเดินอาหารส่วนบนและ 8 รายได้รับการส่องตรวจลำไส้ใหญ่ซึ่งไม่พบความผิดปกติที่สำคัญ ส่วนใหญ่ได้รับการติดตามอาการและไม่พบมีสิ่งผิดปกติที่บ่งชี้ว่าน่าจะมีโรคมะเร็งนี้ ซึ่งรวมถึง 3 รายที่มีระดับโคโมกรานินเอนสูงผิดปกติทั้ง 2 ครั้งด้วย **สรุป:** ความชุกของโคโมกรานินเอนในผู้ป่วยโรคกระเพาะอาหาร โรคไอบีเอส และท้องเสียเรื้อรังในโรงพยาบาลมหาราชนครราชสีมาพบได้สูง แต่ไม่มีส่วนช่วยในการวินิจฉัยโรคมะเร็งนี้ในระยะแรก

## Introduction

Chromogranin A (CgA) or parathyroid secretory protein 1 is an acidic glycoprotein that is widely expressed by neuroendocrine cells (chromaffin cells of the adrenal medulla, paraganglia, enterochromaffin-like cells and beta cells of the pancreas) and can be detected in the blood<sup>(1-3)</sup>. Chromogranin A is the precursor to several functional peptides including vasostatin, pancreastatin, catestatin and parastatin. Nowadays, it is widely accepted

diagnostic markers for neuroendocrine tumors (NETs) with a high specificity and sensitivity<sup>(4)</sup>.

The diagnosis of NETs is often delayed by 5-7 years because the early phase of symptoms is often vague and poorly recognized. Many different clinical presentations of NETs are occasional loose stools, episodic flushing or intermittent abdominal pain which is often misdiagnosed as gastroenteritis, menopause, peptic ulcer disease or irritable bowel disease<sup>(5)</sup>.

In Maharat Nakhon Ratchasima Hospital, we have many patients who presented with dyspepsia, irritable bowel syndrome (IBS) and chronic diarrhea without significant abnormality and had fair symptoms improvement with the treatment. These patients might have early presentation of NETs. The objective is to study the prevalence of chromogranin A in dyspepsia, IBS and chronic diarrhea at Maharat Nakhon Ratchasima Hospital.

## Patients & Methods

### Subjects

All patients (age  $\geq 15$  years) who presented with chronic dyspepsia, IBS and chronic diarrhea at Medical Department of Maharat Nakhon Ratchasima Hospital during February-April 2010 and gave the informed consent to this study were enrolled. The exclusion criteria were chronic renal failure, previous PPI use within 1 week and chronic heart failure.

### Study Design

Three milliliters of blood samples were obtained after overnight fasting and collected in tubes containing EDTA. Within 60 minutes after collection, the samples were centrifuged at 800 rpm with 10-minute duration and the plasma were stored at  $-20^{\circ}\text{C}$  until assayed in central laboratory of Ramathibodi Hospital, Bangkok, Thailand.

The plasma CgA level was measured with ED radioimmunoassay commercially kits (Copenhagen, Denmark). The normal range of CgA by this method is 27-94 ng/ml and positive test is defined if CgA level is more than 94 ng/ml<sup>(4)</sup>.

### Definition of disease study

1. Chronic dyspepsia: dyspeptic symptoms over 3 months
2. IBS: IBS symptoms over 3 months
3. Chronic diarrhea: diarrhea symptom over 1.5 months

### Data Collection

At baseline, the following data were collected: sex, age, address, occupation, body weight, height, smoking, underlying diseases, history of previous drug use according to a doctor orders. The information about the treatment will be happen to follow true state, by have no the share in treatment plan.

### Statistic Analysis

Results are reported in descriptive and plasma CgA level are reported as mean  $\pm$  standard deviation (SD). A *p*-value of less than 0.05 is considered statistically significant.

### Results

During the study period, 84 patients who had chronic dyspepsia, IBS or chronic diarrhea were investigated for plasma CgA test. Nine patients were excluded due to continue PPI use. Finally, 75 patients were enrolled in this study.

The demographic data of this study were shown in table 1. Most of them were female (54 persons; 72%), lived in Nakhon Ratchasima Province (71 persons; 94.7%), no smoking (71 persons; 94.7%) and no alcohol drink (73 persons; 97.3%). Their mean age was  $49.5 \pm 12.1$  years and their occupations were farmer

(28%), worker (26.7%) and government officer (22.7%). Their health service was supported by National Health Service (50.7%), under government service (32%) and social insurance (8%). Most of them (78.7%) had no co-morbid diseases.

**Table 1** Demographic data

	Persons (%) N=75
Female sex	54 (72.0)
Mean age (yrs)	49.5±12.1
Occupation	
- Farmer	21 (28.0)
- Worker	20 (26.7)
- Government officer	17 (22.7)
- Trader	6 (8.0)
- Others	11 (14.7)
Address	
- Nakhon Ratchasima Province	71 (94.7)
- Buriram Province	2 (2.7)
- Chaiyaphum Province	1 (1.3)
- Other	1 (1.3)
Health service profile	
- National health service	38 (50.7)
- Under government service	24 (32.0)
- Social insurance	6 (8.0)
- Other	7 (9.3)
No cigarette smoke	71 (94.7)
No alcohol drink	73 (97.3)
Co-morbid disease	
- No	59 (78.7)
- Chronic HBV or HCV infection	5 (6.7)
- Fatty liver	2 (2.7)
- Tuberculosis of colon or small intestine	2 (2.7)
- Hypertension (HT)	2 (2.7)
- DM & HT	1 (1.3)
- Diabetes mellitus (DM)	1 (1.3)
- Other	3 (4.0)

Majority of samples (86.7%) presented with chronic dyspepsia and median duration of their symptoms was 1 year, as in table 2. Their current medicines were 38 antispasmodic and /or prokinetic drugs, 19 acid blocker without PPI, 7 PPI prior 2 weeks. No aspirin, NSAIDs, clopidogrel or warfarin was taken.

The mean of plasma CgA level was 246±10.9 ng/ml (3 cases which had exceptionally high CgA level more than 870 ng/ml). Of them, 39 patients (52%) had plasma CgA level more than the cut off level.

In high plasma CgA level (positive) group, plasma CgA test was repeated in 11 cases and 3 of them had still

**Table 2** Clinical features and CgA testing

	N=75
Presented disease	
- Chronic dyspepsia	65 (86.7)
- IBS	8 (10.7)
- Chronic diarrhea	2 (2.7)
Median duration of presented diseases (days)	360
Medicine intake	
- Antispasmodic, Prokinetic drugs	38
- Acid blocker except PPI	19
- PPI prior 1 wk	7
- ASA, NSAIDs, Clopidogrel, Warfarin	0
- Others	15
CgA test	
- Negative	36
- Positive (>94 ng/ml)	39 (52.0)*
Mean CgA level (ng/ml)	246±10.9
Follow up duration	
- >2 yrs	24 (32.0%)
- >1 yr	11 (14.7%)
- >6 months	35 (46.7%)
- >3 months	5 (6.6%)

\* >870 in 3 cases

high level (27.3%); >870, 222.3 and 109.9 ng/ml with no PPI intake more than 1 month. The gastroscopy was done in 19 cases and their results were 9 non-specific, 6 *Helicobacter pylori* associated gastritis and 4 normal finding. The colonoscopy was done in 8 cases and all had normal colonoscopic finding. The clinical follow up of all positive group was normal without evidence of NETs, even in 3 cases with persistently positive test.

## Discussion

Neuroendocrine tumors (NETs) are found to be 0.5% of all malignancies and its diagnosis is often delayed and 60-80% of them present with metastatic disease. Five-year survival of NETs with distant metastasis is less than 30%. Early diagnosis and treatment are the best way for improving their survival. Chromogranin A testing is diagnostic markers for neuroendocrine tumors

(NETs) with a high specificity and sensitivity<sup>(4)</sup>. It is also used for follow up or surveillance of cases with previous treated NET especially carcinoid tumors. Its level correlates with the size, extension and the histopathology of NETs. False positive CgA testing occurs in PPI use, rheumatoid arthritis, liver failure, renal failure, atrophic gastritis, pernicious anemia, inflammatory bowel disease, etc.

Our CgA testing was done in 75 patients with mainly chronic dyspepsia. We found that mean CgA level was high ( $246 \pm 10.9$  ng/ml) and positive test was in 39 cases (52% of cases). We also found very high level CgA (>870 ng/ml) in 3 cases (4%). Most of them (93.4%) were followed over 6 months after testing and 46.7% were followed over 1 year duration.

In positive group, repeated CgA testing was done in 11 cases. The persistently positive CgA testing was found in 3 cases (27.3%) without history of PPI intake over 1 month. Their CgA levels were >870, 22.3 and 109.9 ng/ml. In non persistently positive CgA testing (8 cases) group, 5 cases had history of PPI use not more than 1 month. The esophagogastroduodenoscopy was done in 19 cases and their results were normal finding in 4 cases, non-specific gastritis in 9 cases and *Helicobacter pylori* associated gastritis in 6 cases. The colonoscopy was done in 8 cases and all results were normal finding. In this group, most of them were followed up over 6 months duration and 56.4% were followed up over 1 year. The post follow up clinical outcomes of all positive group were normal without evidence of NETs even in 3 cases of persistently positive test.

The prevalence of positive CgA testing in dyspepsia, IBS and chronic diarrhea at Maharat Nakhon Ratchasima Hospital was high but there was no clinical

**Table 3** Further investigations in positive CgA test (n=39)

Repeat CgA test (n=11)	
- Negative	8 (72.7)
- Positive (>94 ng/ml)	3 (27.3)*
Gastroscopy and results (n=19)	
- normal	4
- gastritis	9
- HP associated gastritis	6
Colonoscopy and results (n=8)	
- normal	8
Follow up (n=39)	
- >2 yrs	15 (38.5)
- >1 yr	7 (17.9)
- >6 months	15 (38.5)
- >3 months	2 (5.1)

\* CgA level (>870, 222.3 and 109.9 ng/ml with no PPI intake>1 month)

use for early NETs detection, as compared with the data of Nobels FR et al<sup>(6)</sup>. Nowadays in PPI era, this CgA testing should be cautious in falsely positive result related with PPI use<sup>(7)</sup> and it is suggested that PPI should be discontinued for at least 4 weeks before CgA testing and should be substituted with H<sub>2</sub> blocker.

### Conclusion

The prevalence of positive CgA testing in dyspepsia, IBS and chronic diarrhea at Maharat Nakhon Ratchasima Hospital was high without clinical use for early NETs detection.

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