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Pitfalls in the diagnosis of carcinoid syndrome

Pułapki w diagnostyce zespołu rakowiaka

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Carcinoid syndrome (CS) is a rare syndrome, most commonly associated with neuroendocrine neoplasms (NENs) of the small intestine. Carcinoid syndrome consists of diarrhea, vomiting, abdominal pain, cutaneous flushing, teleangiectasias, bronchoconstriction and increased perspiration. Diagnosis of carcinoid syndrome remains a challenge and it is often delayed.
Objectives. The aim of this study was to characterize patients with CS and define the most sensitive, primary diagnostic tools for CS.
Material and methods. 26 consecutive patients admitted to the Department because of carcinoid-like symptoms. Diagnosis of CS was based on clinical findings and laboratory data (levels of 5-hydroxyindoloacetic acid). Diagnosis of NEN was based on laboratory findings, imaging studies (US, CT, Gallium-68-DOTA TATE PET-CT) and histopathological analysis. CS due to NEN was diagnosed in 16 subjects (NEN–CS).
Results. The most common symptoms in non-NEN were increased perspiration, flushes and diarrhea. CgA was elevated (40%; *n* = 4) in this group. However, elevated levels of 5-HIAA and liver lesions were not presented. In the NEN–CS symptoms were reported more often: flush (93.7%; *n* = 15), diarrhea (87.5%; *n* = 14), abdominal pain and teleangiectasis (81.2%; *n* = 13). Elevated CgA and 5-HIAA were noted in 87.5% (*n* = 14) and 81.2% (*n* = 13) respectively. US and CT revealed liver metastases in all patients. The mean duration of symptoms before diagnosis was 28.6 months.
Conclusions. The combination of several symptoms of carcinoid syndrome and liver lesion in easily available abdominal imaging (US and/or CT) should prompt physicians to quick referral to centres specialized in the diagnosis and treatment of NEN.
Key words: carcinoid syndrome, chromogranin A, 5-HIAA.

Streszczenie **Wstęp.** Zespół rakowiaka (*carcinoid syndrome* – CS) występuje najczęściej w przebiegu nowotworów neuroendokrynnych (*neuroendocrine neoplasms* – NEN) przewodu pokarmowego z ogniskiem pierwotnym w jelicie cienkim. Do głównych objawów należą luźne wypróżnienia, nudności, bóle brzucha, zaczerwienienia twarzy, teleangiektazje, skurcz oskrzeli i wzmożona potliwość. Rozpoznanie zespołu rakowiaka jest najczęściej opóźnione.
Cel pracy. Charakterystyka pacjentów z zespołem rakowiaka i ustalenie podstawowego narzędzia diagnostycznego.
Materiał i metody. Do badania włączono 26 pacjentów przyjętych do Kliniki z powodu objawów zespołu rakowiaka. Diagnostyka CS obejmowała ocenę kliniczną oraz badania dodatkowe (stężenie kwasu 5-hydroksyindolooctowego). Diagnostyka nowotworu neuroendokrynnego obejmowała badania laboratoryjne oraz obrazowe (USG, TK, 68Ga-DOTA TATE PET/CT) oraz badanie histopatologiczne. CS w przebiegu NEN został stwierdzony u 16 pacjentów (NEN–CS).
Wyniki. Najczęściej zgłaszanymi objawami w grupie badanych non-NEN były: wzmożona potliwość, zaczerwienienia twarzy oraz biegunki. Stężenie CgA było podwyższone (40%; *n* = 4) w tej grupie. Nie stwierdzono podwyższenia stężenia kwasu 5-hydroksyindolooctowego i zmian ogniskowych w wątrobie. W grupie NEN–CS najczęściej zgłaszane objawy to odpowiednio: zaczerwienienia twarzy (93,7%; *n* = 15), biegunki (87,5%; *n* = 14), bóle brzucha i teleangiektazje (81,2%; *n* = 13). Podwyższone stężenia CgA i 5-HIAA stwierdzono odpowiednio u 87,5% (*n* = 14) oraz 81,2% (*n* = 13). USG oraz TK wykazały zmiany ogniskowe w wątrobie u wszystkich chorych w tej grupie. Średni czas trwania objawów do rozpoznania NEN wynosił 28,6 miesięcy.
Wnioski. Współwystępowanie objawów zespołu rakowiaka oraz wykonanie jednego z dostępnych badań obrazowych jamy brzusznej (USG lub TK) może być pomocne w ustaleniu rozpoznania wstępnego i przekazaniu chorego do ośrodków specjalistycznych w celu dalszej diagnostyki i leczenia NEN.
Słowa kluczowe: zespół rakowiaka, chromogranina A, 5-HIAA.

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Background

Neuroendocrine neoplasms (NEN) are mainly malignant solid tumours that arise in hormone-secreting tissue of the diffuse neuroendocrine system. Although, traditionally understood as a rare (3/100 000) disease, the incidence and prevalence of NEN are now a more common form of gastrointestinal neoplasms than both esophageal and gastric cancers combined [1]. During the early stages of disease, NEN are generally slow-growing and asymptomatic, but they might have the potential to secrete excessive quantities of bioactive amines, polypeptides and prostaglandins,

other vasoactive substances into the systemic circulation. Few of them (e.g. chromogranin A, CgA, 5-hydroxyindoloacetic acid in 24-hour urine collection test, 5-HIAA) are useful as markers of NEN in diagnostics procedure and follow up [2–4].

Table 1. Baseline characteristics of the patients with carcinoid-like symptoms

Parameter, characteristic		non-NEN (n = 10)	NEN–CS (n = 16)	*p
Sex (F:M ratio)		8:2	10:6	0.4
Age		59.6 ± 12.1 yrs	52.8 ± 11.4 yrs	0.1
GEP-NEN		–	16	
primary tumour of NEN	small intestine	–	12	
	unknown	–	4	
histological grade	G1	–	9	
	G2	–	7	
Ki67 proliferation index		–	2.68	
comorbidity	hypertension	8	9	0.4
	kidney failure	2	3	1.0
	diabetes melitus	2	6	0.4
	gastritis	2	3	1.0
Menopause		7	5	0.1
drugs	calcium channel blockers	1	–	0.4
	nitroglycerine	–	–	
	non-steroidal anti-inflammatory drugs	3	1	0.3
	phosphodiesterase-5 inhibitors	–	–	
	radiological contrast agents	–	–	
	PPI	4	3	0.4
	H_2-blockers	1	1	1.0
	glucocorticosteroids	2	1	0.5

* Fisher Z test, Mann-Whitney U test.

Abbreviations: F – female, GEP-NEN – gastroenteropancreatic neuroendocrine neoplasm, M – male, NEN–CS – positive diagnosis of carcinoid syndrome, non-NEN – negative diagnosis of carcinoid syndrome, PPI – proton pomp inhibitor.

Late in the disease course, typically following tumour metastases to the liver, hormonal hypersecretion can lead to well-defined and debilitating clinical syndromes of CS – diarrhea, stomach cramps and typical flushing, particularly in the face, are the most common (frequency over 75%) symptoms of usually metastasized ileal NEN. As a rule, the flushing starts suddenly and lasts for seconds to a few minutes, often accompanied by burning sensations in the skin and a sensation of heat. The other symptoms of carcinoid syndrome are: teleangiectases, bronchoconstriction, skin changes (pellagra). 40 to 50% of all patients with carcinoid syndrome develop cardiomyopathy with plaque-like fibrosis of the tricuspid and pulmonary valves. This is the most common cause of death in this group of patients.

Diagnosis of carcinoid syndrome remains a challenge and it is often delayed. The differential diagnosis of CS includes physiologic causes, other medical conditions and drugs (Tab. 1). It is most important to identify subjects, who require quick referral to centres specialized in the diagnosis and treatment of NEN. The aim of this study was to review the common manifestations and diagnostic work-up of CS, with a focus on when to suspect CS and when a referral is needed.

Objectives

The aim of the study was to evaluate the symptoms characteristic for carcinoid syndrome and establish their relationship with biomarkers and imaging findings in patients with NEN.

Material and methods

The retrospective study included 26 patients with suspicion of carcinoid syndrome, who was admitted 2009–2014 to Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Poland. They were divided into two subgroups: patients with no tumour found (non-NEN, n = 10) and patients with diagnosis of neuroendocrine neoplasm (NEN–CS, n = 16).

Study protocol

The medical history was taken with a particular attention to the clinical features of carcinoid-like syndrome: flushing, diarrhea, cramping, teleangiectasis, increased perspiration, palpitations, bronchospasm, vomiting, nausea, fever and weight lost. Frequency of symptoms was analyzed in two options: single symptom and ≥ 3 symptoms simultaneously. Furthermore, co-morbidities (hypertension, kidney failure, diabetes mellitus, gastritis) and long-term treatment (calcium channel blockers, nitroglycerine, non-steroidal anti-inflammatory drugs, phosphodiesterase-5 inhibitors, radiological contrast agents, proton pomp inhibitors, H_2--antagonists, glucocoricosteroids), which may have an influence on symptoms or false positive results of non-specific and specific markers, were collected. Additionally, levels of chromogranin A (CgA) and 5-hydroxyindoloacetic acid (5-HIAA) and imaging findings (abdominal ultrasound and triple-phase abdominal computed tomography) were performed. In patients with further suspicion of NEN the Gallium-68-DOTA TATE-PET/CT and ECHO were performed. The diagnosis of gastroenteropancreatic neuroendocrine tumor was proved by histopathology examination after surgery or large needle liver biopsy.

The diagnosis of carcinoid syndrome was based on the ENETS guidelines [5, 6]: 1) clinical features and 2) 5-HIAA in 24-hour urine collection test. Markers: Levels of chromogranin A were measured with enzyme-linked immunosorbent assay CGA-ELISA-US (Cisbio Bioassays, Massachusetts, United States) and 5-HIAA in 24-hours urine collection, acidified, was measured using the LaborLimbach Test (Labor Dr Limbach und Kollegen, Heidelberg, Germany).

Statistical evaluation

Fisher's exact test and Mann-Whitney U test were used to find out the differences in clinical and pathological characteristics in both groups. For multitivariate analysis, odds ratio with 95% confidence intervals was estimated using logistic regression.

Results

The characteristics of patients are presented in Table 1. There were no statistically significant differences in sex, age, co-morbidities and drugs in both groups (Tab. 1).

The differences of symptoms' frequency in investigation subgroups are presented in Table 2. In group with carcinoid syndrome the most common symptoms were flushing and diarrhea, while in non-NEN group – increased perspiration and flushing. All patients in the NEN–CS had ≥ 3 characteristic symptoms simultaneously. The most often symptoms were flushing (93.7%; n = 15), diarrhea (87.5%; n = 14), cramping and teleangiectasia (81.2%; n = 13) – the differences between groups were statistically significant. Four non-NEN patients reported ≥ 3 symptoms simultaneously. However, none of the patients in this group had three or four the most characteristic for carcinoid syndrome symptoms (flushing, diarrhea, cramping and teleangiectasia). The mean duration of symptoms' was similar in both groups.

The mean concentration of chromogranin A (norm < 94 ng/mL) in non-NEN was 128.02 ng/mL, while in NEN-CS was 302.33 ng/mL with no significant difference (p = 0.1). In the non-NEN increased levels of CgA were presented mainly in patients under proton pomp inhibitor therapy and might be false positive. Furthermore, analysis of specific marker for carcinoid syndrome – 5-HIAA in 24-hour urea collection test – presented that the mean value of 5-HIAA (norm < 8 mg/24 h) in the non-NEN was 2.97 mg/24 h and in the NEN–CS was 114.35 mg/24 h. The difference was statistically significant (p < 0.000).

Abdominal ultrasound showed hepatic metastases in the NEN–CS group (93.7%; n = 15). One patient from non-NEN presented lesions in the liver (hemangioma). The results were proved by abdominal and pelvic triple-phase computed tomography scans in both groups. There were no changes in the abdomen in imaging evaluation in non-NEN patient. In the NEN–CS group Gallium-68-DOTA TATE-PET/CT was performed and showed liver lesions with tracer uptake in all patients (Tab. 3). Primary origin of NEN was localized in small intestine in 12 patients (75%) and was remained unknown in 4 patients. Two NEN–CS patients (12.5%) had carcinoid heart disease at the moment of NEN-CS diagnosis.

In standardized multivariate analysis with logistic regression simultaneously of symptoms (OR 22.4; 95 CI 2.06––244.6; p = 0.01), lesions visualised with ultrasound (OR 134.9; 95 CI 7.48–2433; p = 0.009) and elevated 5-HIAA (OR 6.06; 95 CI 0.85–12.9; p = 0.009) were strong predictors of carcinoid syndrome (Tab. 4).

Table 2. Clinical manifestations in patients with carcinoid-like symptoms

		non-NEN n = 10	NEN–CS n = 16	*p
Symptoms % (***n***)	**flushing**	**50.0% (5)**	**93.7% (15)**	**0.0184**
	diarrhea	**40.0% (4)**	**87.5% (14)**	**0.0256**
	cramping	**30.0% (3)**	**81.2% (13)**	**0.0152**
	teleangiectasia	**10.0% (1)**	**81.2% (13)**	**0.0008**
	increased perspiration	60.0% (6)	43.7% (7)	0.7
	palpitations	20.0% (2)	43.7% (7)	0.4
	bronchoconstriction	10.0% (1)	25.0% (4)	0.6
	vomiting	10.0% (1)	6.2% (1)	1.0
	nausea	–	6.2% (1)	1.0
	fever	–	18.7% (1)	0.2
	weight lost	20.0% (2)	31.2% (5)	0.7
≥ 3 symptoms simultaneously		**40.0% (4)**	**100% (16)**	**0.0009**
Duration of symptoms before diagnosis [months]		20.3	28.6	0.3

* Fisher Z test.

Abbreviations: non-NEN – negative diagnosis of carcinoid syndrome, NEN–CS – positive diagnosis of carcinoid syndrome.

Table 3. Laboratory and imaging studies in patients with carcinoid-like symptoms

Investigation	non-NEN (n = 10)	NEN-CS (n = 16)	*p
Laboratory data			
CgA (> normal values)	5	12	0.4
5HIAA (> normal values)	**–**	**13**	**< 0.000**
Imaging studies			
Abdominal ultrasound liver mets	**1**	**15**	**< 0.000**
Abdominal computed liver mets tomography	**–**	**16**	**< 0.000**
Gallium-68-DOTA TATE PET/CT	not performed	16	

*Fisher Z test.

Abbreviations: non-NEN – negative diagnosis of carcinoid syndrome, NEN–CS – positive diagnosis of carcinoid syndrome.

Table 4. Parameters helpful in the diagnosis of carcinoid syndrome							
Parameter	***OR**	***CI 95%**	***p**	**Negative predictive value**	**Positive predictive value**	**Sensitivity**	**Specificity**
≥ 3 symptoms simultaneously	**22.4**	**2.06–244.6**	**0.01**	**85.7%**	**78.9%**	**93.7%**	**60%**
no drugs causing flushing	6.42	0.495–83.46	0.1	36%	0%	0%	90%
CgA (> normal values)	4.33	0.74–25.2	0.1	62.5%	66.6%	75%	50%
5HIAA (> normal values)	6.06	0.85–12.9	0.009	76.9%	100%	81.2%	100%
metastasis in abdominal US	134.9	7.48–2433	0.009	90%	93.7%	93.7%	90%

* Nonlinear estimation: logistic regression analysis.

Discussion

Early diagnosis and treatment of CS due to NEN may enhance the treatment results and significantly improve the quality of life of affected individuals [7–10]. The results of the present study suggest that a combination of clinical symptoms and easy available imaging studies (abdomen US) may be helpful to select the group of patients, who need further investigations of NEN in specialized centres.

In presented material the most common symptoms in non-NEN were increased perspiration and flushing – 60% (n = 6) and 50% (n = 5) respectively. Many of the carcinoid-like symptoms have common benign causes (Tab. 1) – in the present group of non-NEN the causes of flushes might be menopause, non-steroidal anti-inflammatory drugs and calcium channel blockers. In previous studies [11–17], CgA and 5-HIAA are the major and sensitive factors serving for a diagnosis and the follow up. However, it must be remembered that increased levels of CgA may be false positive caused by drugs (e.g. PPI) and co-morbidities (kidney failure, arterial hypertension, cardiac insufficiency, chronic atrophic gastritis, inflammatory diseases). What is more, 5-HIAA levels depend on tumour volume and may be normal either in patients with no-metastatic carcinoid or in patients with low-growing neuroendocrine neoplasm, antidepressants and alcohol usage. [11–17]. In this study, we present that non-specific marker like chromogranin A has limited usefulness in diagnostic procedure. We did not get significant differences in level of CgA between non-NEN and CS–NEN. The increased concentrations of CgA in non-NEN patients were probably false positive according to proton pomp inhibitor usage and co-morbidities (Tab. 5).

The present study suggests that following decisive criteria must be met: 1) simultaneously of carcinoid-like symptoms and 2) well-vascularizied liver lesions to qualify the patient for further diagnostic procedure. Excessive diagnostic procedures may be avoided in patients who are unlikely to have carcinoid syndrome. Recognition of symptoms of carcinoid syndrome and taking prompt action leads to early diagnosis, aiming potentially better outcome. The correct timing for diagnosis and treatment of carcinoid syndrome requires an adequate integration of all available resources of patient care. Despite of advanced diagnostic technique (computed tomography scan, Gallium-68 DOTA TATE positron emission tomography, endoscopic capsule), there is a delay of 3–4 years before correct diagnosis made by the treating physician [18–21]. In the studied group mean time from first symptoms to diagnosis was 28.6 months.

Table 5. Factors of false positive results of CgA and 5-HIAA in group non-NEN		
Results	**Factors**	**non-NEN**
CgA false positive	hypertension	5
	gastritis	1
	PPI	3
5-HIAA false positive	–	0

Abbreviations: non-NEN – negative diagnosis of carcinoid syndrome, PPI – proton pomp inhibitor, CgA – chromogranin A, 5-HIAA – 5-hydroxyindoloacetic acid.

Some important limitations of this study need to be considered: (i) the sample size was relatively small; (ii) CS may be also present in different locations of NEN lung, stomach and ovaries (in these cases, carcinoid syndrome might be presented without any lesions in the liver). Further larger studies using different biomarkers are needed to establish new diagnostic algorithm in order to diagnose CS earlier.

Conclusions

The results of the present study suggest that a combination of clinical (simultaneously of 3 symptoms) and easy available imaging findings (suggesting liver metastasis) are the most important to suspect small intestine NEN with CS. Such patients should be quickly referred to specialized centers.

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