RESEARCH LETTER

Assessment of serotonin concentration in patients with a small-intestine neuroendocrine neoplasm and carcinoid syndrome treated with somatostatin analogues

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Introduction The occurrence of characteristic clinical symptoms depends on the substances secreted by neuroendocrine tumors (NETs). The most common symptoms of the carcinoid syndrome depend on the secretion of serotonin. In the carcinoid cells, serotonin (5-hydroxytryptamine [5-HT]) is synthesized, which begins with the conversion of tryptophan to 5-hydroxytryptophan (5-HTP) catalyzed by tryptophan hydroxylase. In midgut carcinoids, 5-HTP is converted to serotonin by aromatic amino acid decarboxylase, which is stored in the neurotransmission granules or can be released directly into the circulation. A significant portion of serotonin is captured by platelets and stored in their secretory granules. The remainder remains free circulating in plasma and is mainly converted to the 5-hydroxyindoloacetic acid (5-HIAA) metabolite excreted in the urine with the participation of monoamine oxidase and aldehyde dehydrogenase.[1] The reference values of plasma serotonin in healthy people range from 0.1 to 1.1 μmol/l, whereas in patients with carcinoid syndrome, these levels are considerably higher, with an average of 4.5 to 9.5 μmol/l.[2] Vink et al[3] showed that 90% to 94% of 600 patients with carcinoid syndrome had elevated serotonin level, while in a group of 700 asymptomatic patients, these values were increased only in 25% to 50% of individuals. High urinary 5-HIAA levels are found in patients with midgut carcinoid disease. Patients with hindgut carcinoid excreted less 5-HIAA but much more 5-HTP in the urine. In the foregut carcinoid cells, there is probably a deficiency of aromatic amino acid decarboxylase, therefore 5-HTP is secreted into the circulation, where a small fraction is converted into 5-HIAA causing only a slight increase in the urinary concentration of this metabolite. The foregut carcinoid cells usually have low serotonin levels, but release more 5-HTP, histamine, and other hormones. Midgut carcinoids often produce vasomotor substances such as kinins, prostaglandins, and substance P. The secreted amines and peptides by particular carcinoid cells may be different, which is associated with a variety of clinical manifestations. Metastases may secrete other hormones than the original tumor. Moreover, metastases in different locations may secrete various hormones.[4] The aim of this study was to assess serotonin concentrations in patients with carcinoid syndrome treated with somatostatin analogues, depending on the grade of cancer, degree of liver involvement, and stage of the disease.

Patients and methods The study group included 41 people in whom small intestinal NET was diagnosed (women, 29 [70.7%]; men, 12 [29.3%]). The mean (SD) age of men was 60.4 (64.9) years, and of women, 64.2 (74.3) years. All examined patients underwent surgery to remove the primary focus of the neoplasm, with subsequent histopathological assessment according to the 2017 World Health Organization classification. The G1 grade was found in 19 tissue preparations (46.3%), and G2 in the remaining 22 preparations (53.7%). All patients underwent thorough diagnostic imaging (abdominal ultrasound, computed tomography of the chest, abdomen, and pelvis) and supplementary biochemical tests (chromogranin A [CgA], serotonin, and 5-HIAA) to assess the stage of the disease. All patients had liver metastases (10% liver involvement in 23 cases, 25% liver involvement in 18 cases). All patients had carcinoid syndrome and presented with diarrhea, flushing, telangiectasia,

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TABLE 1 Serotonin levels depending on grade, liver involvement, and stage of the disease

Variable		Serotonin, μmol/l					*P* value
		Patients, n	Mean (SD)	Median	Range	IQR	
Tumor grade	G1	19	0.55 (0.26)	0.49	0.20–1.19	0.38–0.63	<0.001
	G2	22	1.85 (1.45)	1.78	0.26–6.08	0.76–2.47	
Tumor grade, last measurement	G1	19	1.04 (0.55)	0.69	0.24–3.68	0.53–0.98	<0.001
	G2	22	3.88 (1.85)	4.37	0.07–10.99	1.55–5.69	
Liver involvement	10%	23	0.53 (0.24)	0.49	0.20–1.19	0.38–0.65	<0.001
	25%	18	2.16 (1.43)	1.88	0.53–6.08	1.18–2.56	
Liver involvement, last measurement	10%	23	0.90 (0.32)	0.66	0.07–3.68	0.43–0.98	<0.001
	25%	18	4.69 (2.55)	4.64	1.17–10.99	2.88–5.84	
Stage of disease	PD	21	1.96 (0.99)	1.79	0.53–6.08	0.85–2.54	<0.001
	SD	20	0.55 (0.21)	0.47	0.20–1.19	0.35–0.55	
Stage of disease, last measurement	PD	21	4.37 (2.52)	4.42	1.17–10.99	2.35–5.76	<0.001
	SD	20	0.66 (0.41)	0.60	0.07–1.97	0.38–0.80	

Abbreviations: IQR, interquartile range; PD, progressive disease; SD, stable disease

and myopathic symptoms. In each case, in order to qualify for treatment with somatostatin analogs, receptor scintigraphy was performed using 99mTc-EDDA / HYNIC-TOC. The rate of radiolabel accumulation in liver metastases was assessed based on a qualitative scale developed by E. Krenning (grade 0–4). In the study group, the degree of accumulation of radiotracer in the liver was in grade 3 and 4 according to the Krenning scale. Patients were treated with somatostatin analogues from 2016 to 2019, receiving LAR octreotide 30 mg (intramuscular injection) or lanreotide 120 mg autogel (subcutaneous injection) every 4 weeks. The control of biochemical parameters such as serum serotonin concentrations, CgA levels, and urinary excretion of 5-HIAA were performed every 3 months. Imaging tests such as abdominal computed tomography were carried out every 6 months in order to obtain an objective assessment of the response to treatment using the RECIST 1.1 criteria. Serum serotonin concentrations were determined by immunoenzymatic ELISA method with the use of Immuno-Biological Laboratories antibodies (Minneapolis, Minnesota, United States).

Written informed consent was obtained from all patients prior to their inclusion in the study. This study was approved by the University Ethics Committee, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis Quantitative variables were analyzed by calculating the mean (SD), median, minimum and maximum value quartiles, and interquartile range. Comparison of quantitative variable values in 2 groups was performed using the Mann–Whitney test. The analysis adopted the significance level of 0.05.

Results

Assessment of serotonin levels according to tumor grade In patients with tumor grade G1, the median serotonin value was 0.49 μmol/l, and in the group with tumor grade G2, it was 1.78 μmol/l (P <0.001). A similar tendency was observed in the analysis of recent serotonin values, namely in the G1 group, the median of the latest serotonin values was 0.69 μmol /l, and in the G2 group, it was 4.37 μmol/l (P <0.001).

Assessment of serotonin levels according to liver involvement The relationship between serotonin levels and liver involvement was also assessed. In the group of patients with 10% liver involvement, the median value of serotonin was 0.49 μmol/l, and in the group with 25% liver involvement, this was higher, 1.88 μmol/l (P <0.001). In the last assessment, serotonin levels in the first group were 0.66 μmol/l, and in the second group, 4.64 μmol/l, respectively (P <0.001).

Assessment of serotonin levels according to the disease stage In the group of patients with disease progression, the median serotonin level was 1.79 μmol/l and it was higher compared with the group with disease stabilization, 0.47 μmol/l (P <0.001). In the analysis of recent levels of serotonin in the group with disease stabilization, the mean was 0.60 μmol/l and it was lower compared with the group with disease progression, where the mean concentration was 4.42 μmol/l (P <0.001). The results of the serotonin concentration assessment are presented in TABLE 1.

Discussion

Our results indicate that serum serotonin values in patients with carcinoid syndrome depend on the tumor grade, stage of the disease, and extent of liver involvement by metastases. In patients with tumor grade G2, mean serotonin values were higher than in the G1 group, as in patients with disease progression and metastatic liver involvement, which translated into exacerbation of carcinoid syndrome symptoms (skin lesions, diarrhea, carcinoid heart disease).

Allen et al[5] reported that determining serotonin and 5-HIAA acid levels is important to

monitor carcinoid syndrome treatment, especially in patients with concomitant carcinoid heart disease. The etiology of the fibrosis process caused by the increased levels of serotonin was described by Druce et al[6] who assessed 45 patients treated for cardiac complications in the course of carcinoid syndrome. Hutcheson et al[7] reported that the tricuspid valve damage is induced by stimulation of the 5-HT2B receptor. Spectacular effects were obtained by using telotristat, which is an inhibitor of serotonin synthesis. Two large clinical trials using this drug, TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) and TELECAST (Telotristat Etiprate for Carcinoid Syndrome Therapy), prove that many clinical symptoms such as diarrhea, facial flushing, or excessive valve fibrosis regress in patients with carcinoid syndrome.[8] These studies also proved that a single measurement of 5-HIAA acid excretion in the morning urine is comparable to 24-hour urine collection.[9] Oberg et al[10] presented completely new biomarkers of neuroendocrine tumors in the form of circulating gene transcripts, micro-RNAs, or tumor cells themselves. The sensitivity and specificity of the above assays is much higher compared with serotonin or CgA assays.[10] Seretis et al[11] presented the role of bombesin as a marker correlating with the histological maturity of the tumor. They reported that the concentration of bombesin in blood serum is higher in cases with lower histological maturity of the tumor. Many studies concerning the treatment of carcinoid syndrome report that very good effects in controlling clinical symptoms are obtained in combination therapy with octreotide and cabergoline.[12] At present, there are no ideal tumor markers used in the treatment and monitoring of neuroendocrine neoplasms, although serotonin and assessment of 5-HIAA acid excretion still appear to be very specific and sensitive markers in the treatment of patients with carcinoid syndrome.

Conclusions Our results indicate that serum serotonin values in patients with carcinoid syndrome depend on the grade of the tumor, stage of the disease, and extent of liver involvement by metastases.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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