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Determination of neuron-specific enolase in patients with midgut-type tumour treated with somatostatin analogues

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Abstract

Introduction: The biochemical diagnosis of neuroendocrine tumours (NETs) uses assays of specific and nonspecific markers. Nonspecific markers include, among others, neuron-specific enolase (NSE). The aim of this study was to evaluate NSE in patients with midgut type tumours treated with somatostatin analogues.

Material and methods: The study group of patients with NETs of the small intestine included 41 patients. Grade G1 was found in 19 cases, while G2 was seen in the remaining 22 cases. Liver metastases were found in all patients studied. The examined group of patients was treated with somatostatin analogues receiving octreotide LAR at a dose of 30 mg. The control of biochemical parameters was performed every 3 months and imaging examinations every 6 months. The Immuno-Biological Laboratories kit was used for determination of NSE concentration, where reference values were 12.5–25 ng/mL.

Results: In the G1 group of patients, the median value of NSE concentration was 134.67 ng/mL, while in the G2 group, the value was 234.55 ng/mL and was significantly higher than in the G1 group ($p = 0.003$). In the determination of NSE concentration values according to the degree of liver involvement, in the group of patients with 10% liver involvement, the median value of NSE concentration was 143.21 ng/mL, while in the group with 25% liver involvement, the value was 251.82 ng/mL ($p < 0.001$). In the analysis of NSE concentration assessment in patients with disease progression, the median value was 234.65 ng/mL compared to the group with disease stabilization, where the median NSE value was significantly lower and amounted to 136.27 ng/mL ($p < 0.001$).

Conclusions: In our study, we observed that NSE concentration values were significantly higher among patients with NET midgut type tumour with histological grade G2 and in patients with 25% liver involvement and progression of the disease process. **(Endokrynol Pol 2021; 72 (4): 308–318)**

Key words: *neuron-specific enolase; neuroendocrine tumours; midgut; somatostatin analogues*

Introduction

The assessment of the endocrine function of gastrointestinal neuroendocrine tumours (NETs) is an important step in the diagnosis and treatment monitoring of these diseases. Specific and non-specific markers of neuroendocrine tumours are used in biochemical diagnostics [1–3]. Non-specific markers include chromogranin A (CgA), neuron-specific enolase (NSE), and the α and β subunits of human chorionic gonadotropin (hCG). NSE has lower sensitivity and specificity in the diagnosis of NETs than CgA [4, 5]. NSE levels are elevated in 50–70% of patients with carcinoid tumour, pancreatic islet tumour, pheochromocytoma, medullary thyroid cancer, and small cell lung cancer [6, 7]. Physiologically, NSE occurs in the central and peripheral nervous system, pituitary, adrenal medulla, and pineal gland. Its elevated values may also be found in septic shock and post-traumatic states. The simultaneous determination of CgA and NSE demonstrates higher sensitivity than of each of these markers separately [8–10]. Neuron-specific enolase is a useful marker in the diagnosis of low and highly differentiated tumours. NSE concentrations roughly correlate with tumour mass and disease stage. Simultaneous determination of CgA, pancreatic polypeptide (PP), and NSE may increase the sensitivity in the diagnosis of NETs, especially endocrine inactive pancreatic NETs and carcinoid tumour [11–12]. Landry et al. present in their work the dependence of NSE levels on tumour size, presence of metastasis to surrounding and distant lymph nodes, histological maturity, and presence of vascular infiltration [13]. The study by Adrichem et al. shows that NSE is a general biomarker of survival in patients with clinical stage IV of NET according to the TNM classification [14]. High NSE values indicate a more aggressive disease course and faster progression. The aim of this study was to evaluate NSE in patients with midgut type tumour treated with somatostatin analogues.

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Material and methods

All examined patients who underwent surgical removal of the primary focus with histopathological evaluation according to the 2017 WHO classification. All patients underwent thorough diagnostic imaging (abdominal ultrasonography, CT scan of chest, abdomen, and pelvis) and complementary biochemical tests like CgA, serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and NSE to assess clinical staging. Receptor scintigraphy with ^{99m}Tc-EDDA/HYNIC-TOC was performed in each case to qualify to treatment with somatostatin analogues. The intensity of radioactive tracer accumulation in liver metastases was evaluated using the qualitative scale developed by E.P. Krenning (grade 0–4) [15]. In the group of patients studied, the degree of radioactive tracer accumulation in the liver was in grades 3 and 4 according to the Krenning scale. The examined group of patients was treated with somatostatin analogues from 2015 to 2019, receiving octreotide LAR at a dose of 30 mg every 4 weeks. The control of biochemical parameters was performed every 3 months. Imaging examinations were performed every 6 months in order to obtain an objective assessment of the response to treatment using RECIST 1.1 criteria. For the determination of NSE levels, a kit from Immuno-Biological Laboratories (Minneapolis, Minnesota, USA) was used, where reference values ranged from 12.5 to 25 ng/mL.

Statistical evaluation

The calculations were made using Statistica 13 by TIBCO and PQStat by PQStat Software. The level of significance was $\alpha = 0.05$. The result was considered statistically significant when $p < \alpha$. The normality of the distribution of variables was tested with the Shapiro-Wilk test. The Wilcoxon-Mann-Whitney-U test was used to compare the variables between the two groups. In order to test whether the changes over time of NSE are statistically significant because of not conforming to the normal distribution, the Friedman ANOVA test was used with the Dunn-Bonferroni multiple comparison test.

Results

The study group of patients diagnosed with NET of the small intestine consisted of 41 patients, including 29 women (70.7%) and 12 men (29.3%). The mean age of males was 60.41 ± 4.90 years while that of females was 64.20 ± 10.39 years. Maturity grade G1 was found in 19 (46.3%) tissue specimens, while G2 (53.7%) was found in the remaining 22 specimens. Liver metastases were found in all patients (10% liver involvement in 23 cases, 25% liver involvement in 18 cases) (Tab. 1). The aim of our study was to assess the concentration of NSE in patients treated with somatostatin analogues. NSE determinations were performed every 3 months. The study was conducted in the period 2015–2019, obtaining 16 NSE determinations for analysis in each patient, which are presented in the attached tables. The results of the study were presented as a comparison of groups of patients depending on the degree of liver involvement, grading, or stage of disease. The changes in the analysed parameters over time were also assessed.

Evaluation of the results of NSE concentration values in relation to grading

In the group of patients with histological tumour maturity grade G1 (n = 19), the median value of NSE concentration was 134.67 ng/mL, while in the group with histological maturity grade G2 (n = 22), this value was 234.55 ng/mL, which was significantly higher than in the G1 group (p = 0.003). An analogous relationship was observed in the analysis of the median of the last NSE concentration values, i.e. in the G1 group the median of last NSE values was 199.67 ng/mL and in the G2 group it was 538.05 ng/mL (p = 0.001) (Tab. 2, 3). The assessment of changes in NSE during therapy showed statistically significant differences in the G1 and G2 groups. In both groups there was an increase in NSE values, but it was significantly faster in the G2 group (Tab. 8, 9) and (Fig. 1–3).

Evaluation of the results of NSE concentration values in relation to the degree of liver involvement

In the analysis of NSE concentration values according to the degree of liver involvement, the median value of NSE concentration in the group of patients with 10% liver involvement (n = 23) was 143.21 ng/mL, while in the group with 25% liver involvement (n = 18) this value was significantly higher and amounted to 251.82 ng/mL (p < 0.001). In the analysis of the last NSE concentration values in the first group, the median of the last values was 221.34 ng/mL, which was significantly lower compared to the second group, in which NSE concentration was 570.73 ng/mL (p < 0.001) (Tab. 4, 5). Analysis of the variables over time showed that the NSE values in patients with liver involvement in 25% increased during treatment with somatostatin analogues much faster and by a higher order of value (Tab. 10, 11) (Fig. 4–6).

Evaluation of NSE concentration results in relation to disease stage

In the analysis of NSE concentration, the median value in the group of patients with disease progression (n = 21) was 234.65 ng/mL compared to the group with disease stabilization (n = 20), where the median value of NSE concentration was significantly lower and equal to 136.27 ng/mL (p < 0.001). On the other hand, in the analysis of the last values, the median NSE concentration in the group with disease progression (PD) was 543.12 ng/mL, which was significantly higher than the group with disease stabilization (SD), in which the NSE concentration value was 210.45 ng/mL (p < 0.001) (Tab. 6, 7). The assessment of NSE values in patients with disease stabilization performed during treatment showed a tendency for a slow increase in the value, but much lower than in the group of patients with disease progression (Tab. 12, 13) (Fig. 7–9).

Table 1. *Characteristics of patients with midgut neuroendocrine tumours*

Number	Patient ID	Gender (F/M)	Age (years)	Primary tumour	Liver involvement by metastasis (%)	Ki-67 (%)	Grading (G1/G2)
1.	2015–01	F	60	Ileum	10	2	G1
2.	2015–02	M	65	Ileum	10	2	G1
3.	2015–03	F	75	Ileum	25	5	G2
4.	2015–04	F	53	Jejunum	25	10	G2
5.	2015–05	F	67	Ileum	10	10	G2
6.	2015–06	M	60	Jejunum	10	4	G2
7.	2015–07	F	73	Jejunum	25	5	G2
8.	2015–08	F	70	Ileum	10	10	G2
9.	2015–09	F	67	Jejunum	10	5	G2
10.	2015–10	F	78	Jejunum	25	10	G2
11.	2015–11	F	55	Ileum	10	1	G1
12.	2015–12	M	60	Ileum	10	4	G2
13.	2015–13	F	69	Ileum	25	5	G2
14.	2015–14	F	49	Ileum	25	10	G2
15.	2015–15	F	73	Jejunum	25	10	G2
16.	2015–16	F	33	Jejunum	10	4	G2
17.	2015–17	F	58	Jejunum	10	2	G1
18.	2015–18	M	61	Ileum	10	2	G1
19.	2015–19	M	65	Ileum	10	2	G1
20.	2015–20	M	66	Jejunum	25	5	G2
21.	2015–21	F	71	Ileum	25	2	G1
22.	2015–22	F	68	Ileum	10	2	G1
23.	2015–23	F	80	Ileum	10	2	G1
24.	2015–24	F	67	Ileum	10	2	G1
25.	2015–25	M	63	Jejunum	10	2	G1
26.	2015–26	F	65	Ileum	25	10	G2
27.	2015–27	F	71	Ileum	10	1	G1
28.	2015–28	M	66	Jejunum	25	10	G2
29.	2015–29	F	67	Jejunum	10	2	G1
30.	2015–30	M	51	Ileum	10	2	G1
31.	2015–31	F	77	Jejunum	25	10	G2
32.	2015–32	F	48	Jejunum	10	2	G1
33.	2015–33	M	54	Ileum	25	5	G2
34.	2015–34	F	65	Jejunum	10	2	G1
35.	2015–35	F	67	Ileum	25	5	G2
36.	2015–36	F	59	Jejunum	25	5	G2
37.	2015–37	F	51	Ileum	25	10	G2
38.	2015–38	M	57	Jejunum	25	10	G2
39.	2015–39	F	61	Ileum	10	2	G1
40.	2015–40	M	57	Jejunum	25	10	G2
41.	2015–41	F	65	Ileum	10	2	G1

Table 2. *Median of neuron-specific enolase (NSE) value depending on grading*

Grading	NSE value [ng/mL]								p*
	N	Mean	SD	Median	Min	Max	Q1	Q3	
G1	19	124.22	61.65	134.67	19.76	229.76	79.45	167.54	0.003
G2	22	254.40	93.35	234.55	62.34	458.32	187.45	324.12	

*Wilcoxon-Mann-Whitney-U test; SD — standard deviation

Table 3. *Median of last neuron-specific enolase (NSE) value depending on grading*

Grading	Last NSE value [ng/mL]								p *
	N	Mean	SD	Median	Min	Max	Q1	Q3	
G1	19	210.41	104.53	199.67	30.13	436.78	127.76	265.45	0.001
G2	22	483.22	161.09	538.05	87.98	673.45	352.12	621.12	

*Wilcoxon-Mann-Whitney-U test; SD — standard deviation

Table 4. *Median of neuron-specific enolase (NSE) value depending on the degree of liver involvement*

Liver involvement degree	NSE value [ng/mL]								p*
	N	Mean	SD	Median	Min	Max	Q1	Q3	
10%	23	134.69	61.38	143.21	19.76	229.76	86.55	180.54	< 0.001
25%	18	269.95	95.96	251.82	62.34	458.32	210.87	324.12	

*Wilcoxon-Mann-Whitney-U test; SD — standard deviation

Table 5. *Median of last neuron-specific enolase (NSE) value depending on the degree of liver involvement*

Liver involvement degree	Last NSE value [ng/mL]								p*
	N	Mean	SD	Median	Min	Max	Q1	Q3	
10%	23	223.91	98.87	221.34	30.13	426.67	153.21	278.76	< 0.001
25%	18	526.60	145.55	570.73	87.98	673.45	456.23	623.21	

*Wilcoxon-Mann-Whitney-U test; SD — standard deviation

Table 6. *Median of neuron-specific enolase (NSE) value depending on the stage of the disease*

Stage of disease	NSE value [ng/mL]								p*
	N	Mean	SD	Median	Min	Max	Q1	Q3	
PD	21	259.07	93.28	234.65	62.34	458.32	210.87	324.12	< 0.001
SD	20	125.83	59.95	136.27	19.76	229.76	83.00	172.94	

*Wilcoxon-Mann-Whitney-U test; PD — progressive disease; SD — stable disease; SD — standard deviation

Table 7. *Median of last neuron-specific enolase (NSE) value depending on the stage of the disease*

Stage of disease	Last NSE value [ng/mL]								p*
	N	Mean	SD	Median	Min	Max	Q1	Q3	
PD	21	499.92	151.79	543.12	87.98	673.45	421.34	621.12	< 0.001
SD	20	206.51	91.11	210.45	30.13	426.67	140.48	270.84	

*Wilcoxon-Mann-Whitney-U test; PD — progressive disease; SD — stable disease; SD — standard deviation

Table 8. *Neuron-specific enolase (NSE) concentrations in patients with grading G1*

The number of NSE determinations at intervals of 3 months	ANOVA Friedman Test and Kendall's compliance factor χ^2 test, ANOVA (N = 19, df = 15) = 282.1391 p = 0.00000 Kendall's compliance factor = 0.98996 Group of patients with grading G1			
	Mean rank	Total rank	Mean	SD
NSE 1	1.00000	19.0000	57.7147	41.5644
NSE 2	2.42105	46.0000	74.1505	48.1867
NSE 3	2.84211	54.0000	80.3674	46.2400
NSE 4	3.84211	73.0000	87.4858	47.1748
NSE 5	5.00000	95.0000	96.7147	50.5468
NSE 6	6.18421	117.5000	107.7821	54.4278
NSE 7	6.89474	131.0000	113.7668	57.5935
NSE 8	7.81579	148.5000	124.2274	61.6521
NSE 9	9.05263	172.0000	133.2142	64.3455
NSE 10	9.94737	189.0000	143.3568	68.9360
NSE 11	11.05263	210.0000	154.8663	76.8494
NSE 12	12.05263	229.0000	164.3074	81.8665
NSE 13	12.94737	246.0000	178.8311	88.4108
NSE 14	14.05263	267.0000	190.0758	92.4878
NSE 15	15.05263	286.0000	202.0116	98.4470
NSE 16	15.84211	301.0000	210.4174	104.5348

SD — standard deviation

Table 9. *Neuron-specific enolase (NSE) concentration in patients with grading G2*

The number of NSE determinations at intervals of 3 months	ANOVA Friedman Test and Kendall's compliance factor χ^2 tes, ANOVA (N = 22, df = 15) = 325.7767 p =0.00000 Kendall's compliance factor = 0.98720 Group of patients with grading G2			
	Mean rank	Total rank	Mean	SD
NSE 1	1.04545	23.0000	104.9009	72.7653
NSE 2	1.95455	43.0000	120.6795	73.9144
NSE 3	3.00000	66.0000	139.5950	74.1617
NSE 4	4.04545	89.0000	165.4005	82.9654
NSE 5	5.04545	111.0000	185.1473	87.1361
NSE 6	6.04545	133.0000	208.9973	89.2591
NSE 7	6.86364	151.0000	233.1536	95.2373
NSE 8	8.04545	177.0000	254.4064	93.3510
NSE 9	9.04545	199.0000	282.9327	97.5109
NSE 10	10.13636	223.0000	311.7505	104.1570
NSE 11	11.27273	248.0000	334.4173	110.6949
NSE 12	11.86364	261.0000	355.7800	122.4481
NSE 13	13.00000	286.0000	387.9255	135.0418
NSE 14	13.90909	306.0000	414.4964	144.1943
NSE 15	14.81818	326.0000	454.1450	155.7836
NSE 16	15.90909	350.0000	483.2236	161.0939

SD — standard deviation

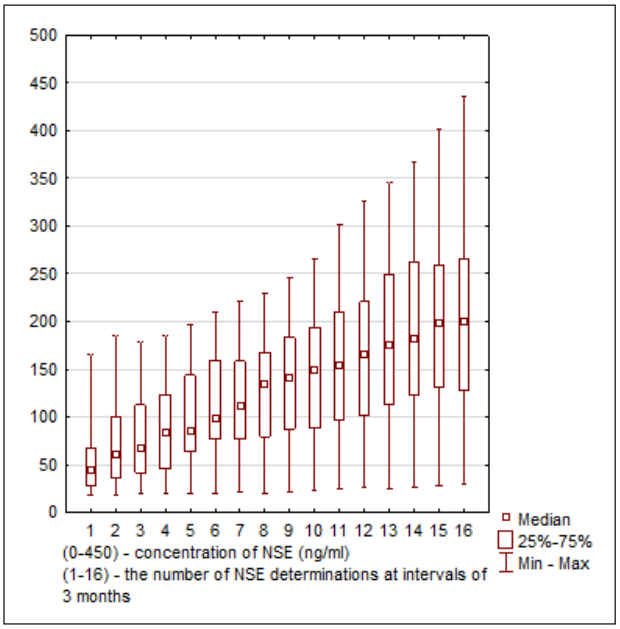

Figure 1. *Neuron-specific enolase (NSE) concentrations in patients with G1 grading*

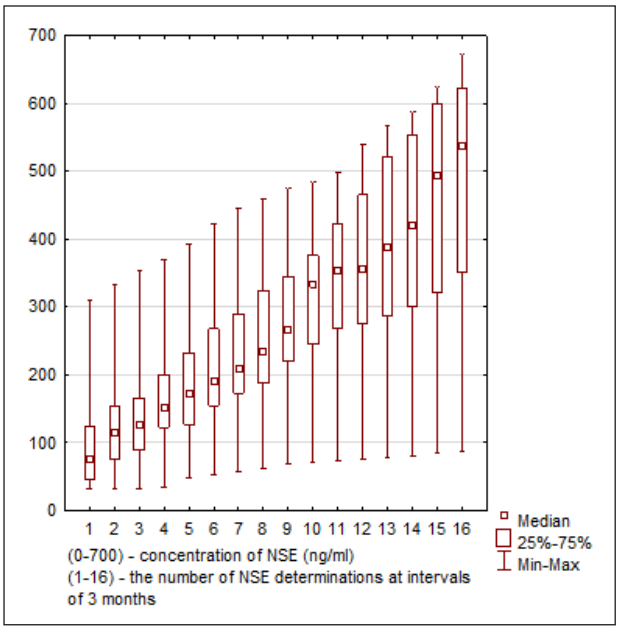

Figure 2. *Neuron-specific enolase (NSE) concentrations in patients with G2 grading*

Discussion and Conclusions

In our study, we observed that NSE concentration values were significantly higher among patients with histological maturity of neuroendocrine tumour grade G2 and in patients with 25% liver involvement and progression of the disease process. NSE may be elevated in 38–45% of low-grade NETs, and it is one of the important prognostic factors. We also noticed that

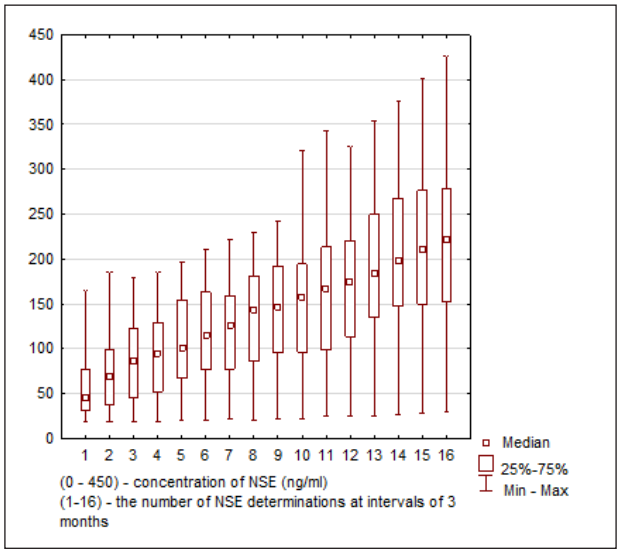

Figure 3. *Neuron-specific enolase (NSE) concentrations in patients with G1 and G2 grading*

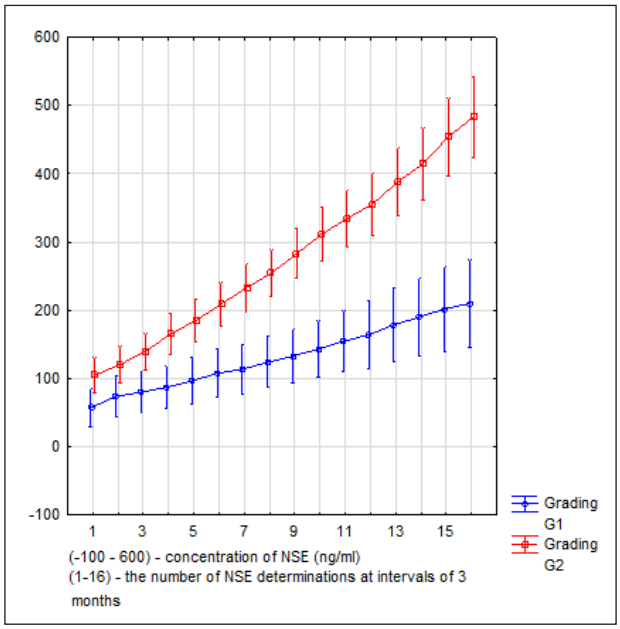

Figure 4. *Neuron-specific enolase (NSE) concentrations in patients with 10% liver involvement*

in all groups of patients undergoing treatment with somatostatin analogues an increase in NSE values was seen. It is worth noting that the increase in NSE was statistically greater in patients with disease progression, 25% liver involvement, or G2 grading. The level of NSE correlates with tumour differentiation, aggressiveness, and tumour size and is inversely related to general survival and progression-free survival [16]. It is currently believed that the NSE level depends on the presence of metastases, their location, number, and size and correlates with response to treatment with

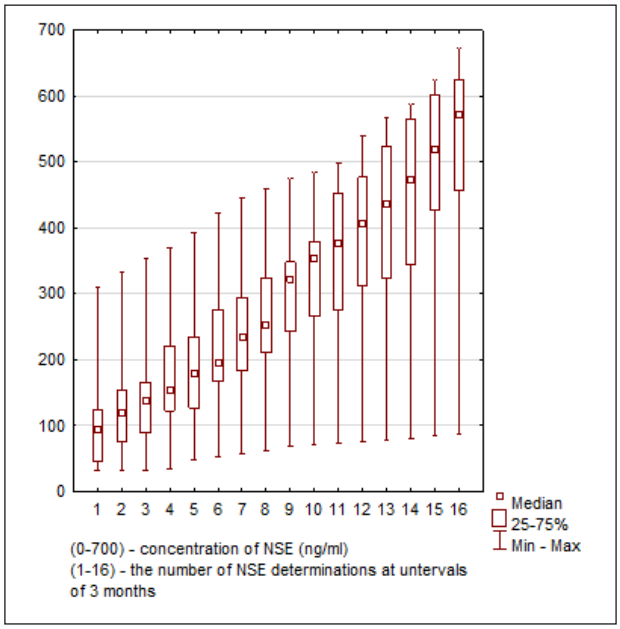

Figure 5. *Neuron-specific enolase (NSE) concentrations in patients with 25% liver involvement*

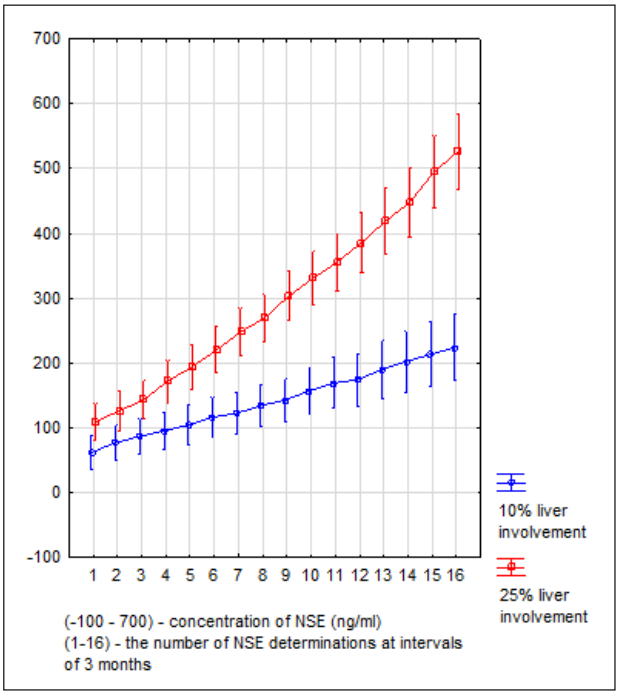

Figure 6. *Neuron-specific enolase (NSE) concentrations in patients with 10% and 25% liver involvement*

somatostatin analogues [17]. The authors of many reports show that the values of NSE in patients with neuroendocrine neoplasms tend to increase during treatment [18, 19]. The rate of increase in concentration or the time to double the value depends on the degree of malignancy and the course of the disease. It has been proven that faster NSE increases occur in patients with G2 or G3 grading and with high liver

Table 10. *Neuron-specific enolase (NSE) concentrations in patients with 10% liver involvement*

The number of NSE determinations at intervals of 3 months	ANOVA Friedman Test and Kendall's compliance factor χ^2 test, ANOVA (N = 23, df = 15) = 337.9561 p = 0.00000 Kendalls' compliance factor = 0.97958 Group of patients with 10% liver involvement			
	Mean rank	Total rank	Mean	SD
NSE 1	1.00000	23.0000	62.3422	43.27264
NSE 2	2.34783	54.0000	77.6848	47.15279
NSE 3	2.86957	66.0000	87.4813	46.70559
NSE 4	3.91304	90.0000	95.7813	48.60537
NSE 5	5.04348	116.0000	104.8413	51.00891
NSE 6	6.19565	142.5000	116.5817	54.36883
NSE 7	6.78261	156.0000	122.8222	57.09912
NSE 8	7.89130	181.5000	134.6974	61.38782
NSE 9	9.08696	209.0000	143.1761	63.00154
NSE 10	10.08696	232.0000	157.4835	75.31124
NSE 11	11.30435	260.0000	169.3274	81.67059
NSE 12	11.91304	274.0000	174.3604	78.56607
NSE 13	12.95652	298.0000	190.8513	85.52316
NSE 14	13.95652	321.0000	202.7343	89.72118
NSE 15	14.86957	342.0000	213.7426	93.84824
NSE 16	15.78261	363.0000	223.9122	98.87586

SD — standard deviation

Table 11. *Neuron-specific enolase (NSE) concentrations in patients with 25% liver involvement*

The number of NSE determinations at intervals of 3 months	ANOVA Friedman Test and Kendall's compliance factor χ^2 test, ANOVA (N = 18, df = 15) = 269.9167 p = 0.00000 Kendall's compliance factor = 0.99969 Group of patients with 25% liver involvement			
	Mean rank	Total rank	Mean	SD
NSE 1	1.05556	19.0000	109.4739	77.2166
NSE 2	1.94444	35.0000	126.5033	78.8214
NSE 3	3.00000	54.0000	143.6667	80.3969
NSE 4	4.00000	72.0000	172.1150	89.3396
NSE 5	5.00000	90.0000	194.4150	92.9599
NSE 6	6.00000	108.0000	220.2456	94.4134
NSE 7	7.00000	126.0000	248.1133	98.5946
NSE 8	8.00000	144.0000	269.9567	95.9628
NSE 9	9.00000	162.0000	303.4744	95.7778
NSE 10	10.00000	180.0000	331.1206	100.9483
NSE 11	11.00000	198.0000	355.8394	106.9080
NSE 12	12.00000	216.0000	385.4839	114.6341
NSE 13	13.00000	234.0000	419.0317	128.9639
NSE 14	14.00000	252.0000	448.1928	136.8991
NSE 15	15.00000	270.0000	495.1850	141.1335
NSE 16	16.00000	288.0000	526.6039	145.5583

SD — standard deviation

Table 12. *Neuron-specific enolase (NSE) concentrations in patients with stable disease (SD)*

The number of NSE determinations at intervals of 3 months	ANOVA Friedman Test and Kendall's compliance factor χ^2 test, ANOVA (N = 20, df = 15) = 295.9596 p = 0.00000 Kendall's compliance factor = 0.98653 Group of patients with SD			
	Mean rank	Total rank	Mean	SD
NSE 1	1.00000	20.0000	55.9090	39.20011
NSE 2	2.40000	48.0000	71.5840	45.69266
NSE 3	2.85000	57.0000	80.6815	44.60210
NSE 4	3.90000	78.0000	88.3710	46.70542
NSE 5	5.05000	101.0000	96.5590	48.72696
NSE 6	6.22500	124.5000	107.5600	51.89274
NSE 7	6.75000	135.0000	113.3280	54.22080
NSE 8	7.87500	157.5000	125.8365	59.95579
NSE 9	9.10000	182.0000	134.8905	62.35193
NSE 10	9.85000	197.0000	143.9380	66.76366
NSE 11	11.10000	222.0000	154.4945	71.91771
NSE 12	12.00000	240.0000	161.8815	73.80538
NSE 13	13.05000	261.0000	176.8930	81.19302
NSE 14	14.05000	281.0000	186.4670	83.16072
NSE 15	14.95000	299.0000	196.7600	86.16215
NSE 16	15.85000	317.0000	206.5180	91.11139

SD — standard deviation

Table 13. *Neuron-specific enolase (NSE) concentrations in patients with progressive disease (PD)*

Number of NSE determinations at intervals of 3 months	ANOVA Friedman Test and Kendall's compliance factor χ^2 test, ANOVA (N = 21, df = 15) = 311.9748 p = 0.00000 Kendall's compliance factor = 0.99040 Group of patients with PD			
	Mean rank	Total rank	Mean	SD
NSE 1	1.04762	22.0000	108.8676	73.1644
NSE 2	1.95238	41.0000	125.3395	73.9349
NSE 3	3.00000	63.0000	142.1162	75.2625
NSE 4	4.00000	84.0000	168.2676	83.5643
NSE 5	5.00000	105.0000	189.5067	87.0499
NSE 6	6.00000	126.0000	214.0286	88.8238
NSE 7	7.00000	147.0000	239.2567	94.1239
NSE 8	8.00000	168.0000	259.0729	93.2857
NSE 9	9.00000	189.0000	288.4657	96.7623
NSE 10	10.23810	215.0000	319.2157	100.7601
NSE 11	11.23810	236.0000	343.3214	106.9528
NSE 12	11.90476	250.0000	367.2081	117.0264
NSE 13	12.90476	271.0000	399.7281	129.5134
NSE 14	13.90476	292.0000	428.6200	136.3811
NSE 15	14.90476	313.0000	471.1529	144.8923
NSE 16	15.90476	334.0000	499.9281	151.7909

SD — standard deviation

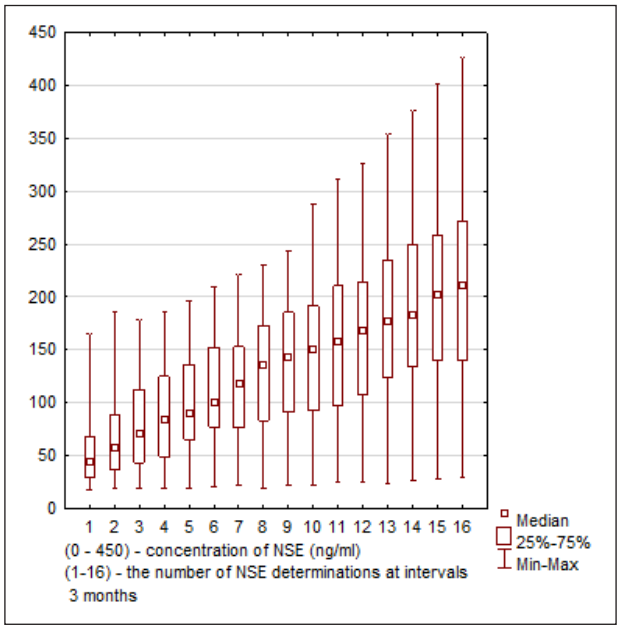

Figure 7. *Neuron-specific enolase (NSE) concentrations in patients with stable disease (SD)*

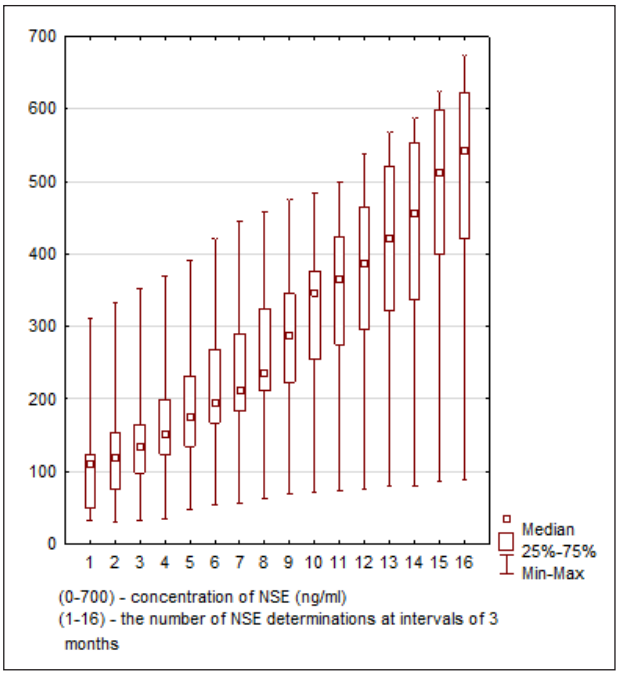

Figure 8. *Neuron-specific enolase (NSE) concentrations in patients with progressive disease (PD)*

involvement [20, 21]. At the same time, it should be added that NSE is not an ideal marker of neuroendocrine tumours. Its elevated values are also found in small cell lung cancer, neuroblastoma, malignant melanoma, brain tumours, or inflammation of the central nervous system [22]. Mijones et al. noted that tumour cells with NSE expression are most commonly

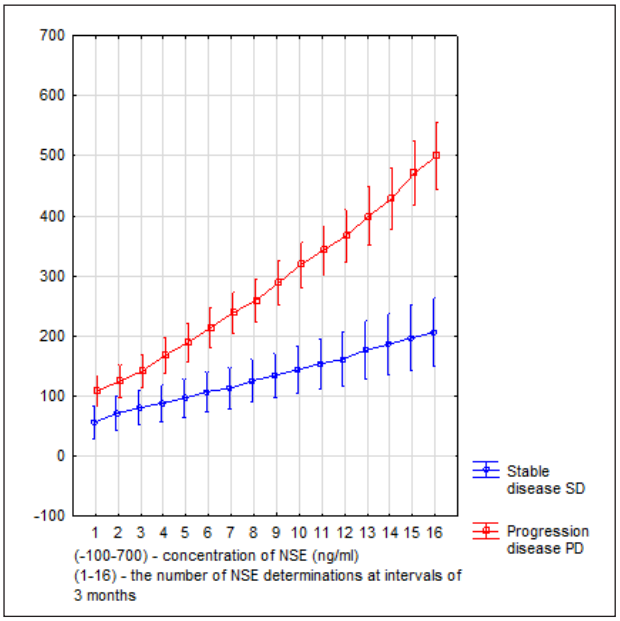

Figure 9. *Neuron-specific enolase (NSE) concentrations in patients with stable (SD) and progressive disease (PD)*

observed in NETs and renal cell carcinoma. A positive relationship was found between NSE expression and the number of additional neuroendocrine markers expressed in a given tumour, such as CgA, chorionic gonadotropin, and synaptophysin [23]. Similar observations were reported by Bajetta et al., considering that NSE values described in patients with carcinoid tumour are dependent on CgA levels and 5-HIAA excretion. Simultaneous determination of NSE and 5-HIAA showed very high specificity (100%) but low sensitivity (32.9% and 35.1%, respectively). Moreover, the results of the above study show that CgA and NSE have the highest sensitivity and most reliable accuracy reflecting the clinical stage of NETs [24]. Completely different findings were described by Manfe et al. evaluating CgA, NSE, and 5-HIAA in small intestinal neuroendocrine tumours with maturity stage G2. The specificity of CgA, NSE, and 5-HIAA was 86%, 87%, and 93%, and the sensitivity was 64%, 36%, and 35%, respectively. No relationship was found between survival and 5-HIAA excretion and serum NSE levels [25]. In conclusion, it should be emphasized that NSE is one of the key non-specific markers used in the diagnosis and treatment monitoring of neuroendocrine tumours. The sensitivity and specificity of NSE determination is highly applicable in patients with more advanced and aggressive forms of the disease. It is also worth mentioning that the value of NSE determination is significantly higher in correlation with the assessment of other additional markers such as: CgA, 5-HIAA, or synaptophysin.

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