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Leptin concentration in children with juvenile idiopathic arthritis

Stężenie leptyny u dzieci z młodzieńczym idiopatycznym zapaleniem stawów

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Abstract

Introduction: Leptin regulates the organism's immune response. Juvenile idiopathic arthritis (JIA) is a chronic joint disease in children, leading to chronic changes in motor organs.

Material and methods: In children with JIA (n = 42) and healthy subjects (n = 28), leptin concentration (LEP), body mass index (BMI), haematocrit (HTC), haemoglobin (HB), morphotic elements (WBC,LYMPH), erythrocyte sedimentation rate (ESR), and ANA Hep-2 antibodies were analysed. JIA group was divided into: children with a longer (51–148 months) (IA) n = 22 and a shorter disease period (2-18 months) (IB) n = 20.

Results: Only 58.3% of the IA and 50% of the IB group had ANA Hep-2 confirmed. The ill children had higher and more diversified LYMPH and ESR levels compared to the healthy children. The highest LEP for the IA group was 37.5 ng/cm^3, (Me 5.85), for IB — 40.10 ng/cm^3, (Me 2.46) as compared to the IC — 3.74 ng/cm^3 (Me 2.85), respectively. The average BMI value for the IA group was 16.61 kg/m^2, for IC it was 18.91 kg/m^2, and the median for IB was 15.89 kg/m^2. Children with BMI values < 23 kg/m^2 from the IA and IB group had a reduction in LEP as compared to control group (p = 0.04). The relationship between the illness and LEP diversification per BMI unit was found in both groups. Children with a shorter illness period had higher LEP differentiation per BMI unit compared to the healthy children.

Conclusions:

1. Children with juvenile idiopathic arthritis with BMI < 23 kg/m^2 had lower leptin concentrations than healthy subjects.
2. Ill children with a shorter-term disease had a higher diversification of leptin concentration per BMI unit as compared to healthy controls.

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Key words: *juvenile idiopathic arthritis; leptin; BMI*

Streszczenie

Wstęp: Leptyna reguluje odpowiedź immunologiczną organizmów. Młodzieńcze idiopatyczne zapalenie stawów (MIZS) jest przewlekłą chorobą stawów u dzieci prowadzącą do przewlekłych zmian w narządach układu ruchu.

Materiał i metody: U dzieci z MIZS (n = 42) i zdrowych osobników (n = 28) analizowano następujące parametry: stężenie leptyny (LEP), wskaźnik masy ciała (BMI), hematokryt (HTC), zawartość hemoglobiny (HB), liczba elementów morfotycznych krwi (WBC, LYMPH), odczyn OB i obecność przeciwciał ANA Hep-2. Grupę MIZS podzielono na: dzieci dłużej chorujące (51–148 miesięcy) n = 22 (IA) i krócej chorujące (2–18 miesięcy) n = 20 (IB).

Wyniki: Tylko u 58,3% dzieci grupy IA i 50% dzieci grupy IB potwierdzono obecność przeciwciał przeciwjądrowych ANA Hep-2. U chorych dzieci wykazano wyższe poziomy LYMPH i OB oraz większe zróżnicowanie wyników, w porównaniu do dzieci zdrowych. Najwyższe stężenie LEP dla grupy IA wynosiło 37,50 ng/cm^3, (Me 5,85) dla IB 40,10 ng/cm^3, (Me2,46), w porównaniu z IC, gdzie wynosiło odpowiednio 3,74 ng/cm^3 (Me 2,85). Średnia wartość BMI dla grupy IA wynosiła 16,61 kg/m^2, dla IC 18,91 kg/m^2, a mediana dla IB 15,89 kg/m^2. U dzieci z BMI < 23 kg/m^2, grupy IA i IB, stwierdzono niższe stężenia leptyny w porównaniu z grupą kontrolną (p = 0,04). Stwierdzono wpływ schorzenia na zróżnicowanie stężenia leptyny w przeliczeniu na BMI w obu grupach dzieci chorych. U chorych dzieci, z krótszym czasem trwania choroby, wykazano większe zróżnicowanie wartości stężenia leptyny w przeliczeniu na BMI, niż u zdrowych.

Wnioski:

1. Dzieci z młodzieńczym idiopatycznym zapaleniem stawów z BMI<23 kg/m^2 mają niższe stężenie leptyny niż dzieci grupy kontrolnej.
2. Dzieci z MIZS z krótszym czasem trwania choroby, charakteryzują się większym zróżnicowaniem stężenia leptyny w przeliczeniu na jednostkę BMI, w porównaniu ze zdrowymi dziećmi. **(Endokrynol Pol 2015; 66 (5): 417–421)**

Słowa kluczowe: *młodzieńcze idiopatyczne zapalenie stawów; leptyna; BMI*

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Introduction

The obesity gene (ob) is responsible for proleptin biosynthesis, the leptin precursor. Leptin generation mainly occurs in subcutaneous adipose tissue adipocytes and in the placenta trophoblast; it may be also synthesised in gastric epithelial cells and in the female mammary glands. Its small distribution has been confirmed in areas of the hypothalamus, pituitary gland, liver, and striated tissue [1–4]. One of its lesser-known functions is its immune system regulatory function. Leptin reduction due to adipose tissue decrease or nutritional restrictions may cause immune disorders and may increase the risk of contagious diseases by affecting acquired and inborn immunity or by stimulating both pro- and anti-inflammatory effects [5, 6]. Leptin intensifies the inflammatory response by monocyte and macrophage activation, which, under its influence, increases production of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6 [7–9]; it also regulates growth, proliferation, and activation of T lymphocytes. Leptin also affects direct T cell differentiation to the Th1 phenotype, which intensifies inflammation by releasing IL-2 and interferon G, as well as prevents steroid-induced lymphocytes apoptosis [6, 10, 11]; however, it also has certain anti-inflammatory properties, which are related to IL-1 receptor antagonist release [6].

Due to the double role of leptin in the inflammatory process, it is difficult to assess its total impact on immune response. Leptin performs different functions on acute and chronic inflammations, as it has been observed at increased concentrations during acute inflammation, such as in sepsis or in septic shock. The released cytokines stimulate leptin production in the adipocytes, where leptin causes cytokine post-inflammatory effects by its intensified production in macrophages, thus giving patients a greater chance to survive acute inflammation [3, 6, 12]. There are, however, data indicating that chronic inflammatory diseases may cause a reduction in leptin concentration, perhaps due to the fact that long-term adipose tissue stimulation with pro-inflammatory cytokines limits leptin production [13–15].

Juvenile idiopathic arthritis (JIA) is a chronic joint disease starting before the age of 16 and lasting for at least 6 weeks or 3 months and causing chronic changes to motor organs [16–18]. Due to improper anti-inflammatory functioning in rheumatic disease, macrophage and T lymphocyte activation occurs which causes pro- and anti-inflammatory factor balance disruption, the consequence of which is activation of other immune system cells and inflammatory processes [19, 20].

The aim of the study was to assess leptin concentration, body mass index, haemoglobin, morphotic elements, and ANA Hep-2 antibodies in children with juvenile idiopathic arthritis (JIA).

Material and methods

The tests in this study were performed on a group of 42 children with JIA across different ages; 28 healthy children (IC) constituted the control group. The study was approved by the Local Committee of Bioethics. All ill children received a non-steroidal anti-inflammatory drug (methotrexate).

The children were divided into two subgroups: the IA group consisted of children with a longer disease period (51–148 months) and the IB group consisted of children with a shorter disease period (2–18 months). The children from the IA group were between 7 and 18 years old (average: 13 years old), the children from the IB group were between 4 and 17 years old (average: 10 years old), and the children in the control group were between 8 and 15 years old (average: 11 years old). The nutritional condition of the examined groups was assessed by body mass index (BMI) calculation kg/m^2. During the tests, venous blood was collected from the children, of which the following indicators were determined: haematocrit (HTC), haemoglobin (HGB), erythrocyte sedimentation rate (ESR), and concentrations of leukocytes and lymphocytes (WBC and LYMPH). LEP was determined and tests for ANA Hep-2 antinuclear antibodies were also performed. For test purposes, elbow vein blood was taken and put through three kinds of Vacutainer test tubes; two of them contained anticoagulants (EDTA-K_2 solution or 3.8% sodium citrate solution) that prevent blood clotting.

In the EDTA-K_2 solution-containing tests HTC, WBC was determined, whereas in sodium citrate solution-containing tests, ESR was determined. WBC quantity and HB content in the analysed samples was assessed with the use of a haematology analyser, BC 2300. ESR was assessed from erythrocyte sedimentation time in Westergen tubes from blood collected and mixed with 3.8% sodium citrate solution (4:1). This assessment was made one hour after putting a given sample on a rack and was calculated in mm/h.

In order to obtain serum, blood was kept from clotting in room temperature for 30 min. and centrifuged in 3000 rpm for 15 min. at 4 ± 2°C, after which the serum was separated and put into clean test tubes. Then, it was examined for LEP and the presence of ANA-Hep2 antinuclear antibodies. LEP was measured using an ELISA test designed by LINCO Research Inc. LEP in the tested samples was determined on the basis of a reference curve interpolation created by the same analysis with the use of a standard solution of human leptin in at concentrations of 1–100 ng/cm^3. The presented results are average values from three analyses.

For the tests on ANA-Hep2 antinuclear antibodies in serum, the Colorzyme HEp-2 ANA test of Immuno

Concepts N.A. Ltd. was used, which consisted of antinuclear antibodies identification by indirect immunofluorescence and observing characteristic luminosity in fluorescent microscope, confirming the presence of autoantibodies.

In order to determine the relationships between random variables, LEP, illness duration, sex, age, and BMI, as well as WBC, LYMPH, HBG, HCT, and ESR, were assessed and parametric methods were used (single direction ANOVA, *t* test for independent groups, and Pearson's linear correlation coefficient,) as well as non-parametric methods (Kruskal-Wallis ANOVA test and median test, Mann-Whitney U test, Kolmogorov-Smirnov test, Waldo-Wolfowitz test, ranks correlations, ranks correlation Spearman coefficient, τ Kendall test, and Fisher's exact test). The following correlations were also tested: LEP, LEP/BMI, LEP/age, and LEP/ /time, as well as WBC, LYMPH, HBG, HCT, and ESR in the healthy and ill children (longer illness period: IA; shorter illness period: IB). The relationship between health conditions (healthy, ill IA, and IB) was assessed using the following measurements: WBC, LYMPH, HBG, HCT, and ESR. The differences between LEP values within general populations of ill (IA+IB) and healthy children (IC) as well as between IA and IC and IB and IC were also examined. For all statistical analyses the $\alpha = 0.05$ significance level was determined.

Tests were also carried out to assess the effect of BMI on LEP values. The difference in LEP value per BMI unit LEP/BMI was evaluated for the healthy and ill children. The correlation between LEP, LEP/BMI, and age, as well as LEP, LEP/BMI, and disease period, was assessed either in healthy or ill children (IA, IB). The influence of health condition on LEP/age was assessed in the healthy (IC) and ill children (IA, IB), as well as in the healthy (IC) and ill children (IA + IB). The relationship between LEP and BMI was estimated (IA + IB + IC).

On the basis of scientific writing, the LEP standard value for the following group of children was determined: BMI < 23 kg/m^2 — below 5 ng/cm^3. Based on this value, LEP normal values were assessed (exclusively BMI < 23 kg/m^2), as well as those that exceeded this standard. The relationship between health condition (healthy, ill) and LEP (standard, increased) was determined [23–25].

Results

Antinuclear antibodies (ANA) were determined for 58.3% of the IA group children and for 50% of the IB group children, but antibodies were not detected in the control group.

The effect of health condition on the random variable LYMPH was established, with assumed validity level α: Kruskal-Wallis test H = 17.3, p = 0.0002; median test, $\chi^2 = 11.4$, p = 0.003. On the basis of *p* value estimation for multiple (collateral) comparisons, we found that there is a statistical validity of difference between tested healthy (IC) and ill child populations (IA) ($p < 0.0003$) as well as between tested healthy (IC) and ill child populations (IB) ($p < 0.003$), considering the LYMPH random variable for assumed α validity.

The effect of a health condition on the ESR random variable was proven, with assumed α validity: Kruskal-Wallis test H = 14.9, p = 0.0006; median test, $\chi^2 = 8.96$, p = 0.011. On the basis of p value assessment for multiple (collateral) comparisons, it was proven that there is statistical validity between tested healthy (IC) and ill children (IA) ($p < 0.0008$), as well as between healthy (IC) and (IB) ill children ($p < 0.006$), considering the ESR random variable, with assumed α validity.

The results and relationships obtained are shown in Table I. The highest LEP value in the IA group was 37.50 ng/cm^3 and the lowest was 1.24 ng/cm^3. In the serum of children from the IB group these concentrations came to 40.1 ng/cm^3 and 0.93 ng/cm^3, respectively. In the control group the highest LEP value was 3.74 ng/cm^3 and the lowest was 2.4 ng/cm^3.

Using a *t* test for independent samples, for non-homogeneous variances, a statistical validity of LEP random variables was determined in ill children (IA and IB) with a BMI < 23 kg/m^2, as well as the population of healthy children, for assumed validity level α (p = 0.04). The statistical feature of LEP difference values for samples taken from the tested populations was –0.91. The difference of expected LEP random variables in the tested population of ill children (B) with a BMI < 23 kg/m^2 and healthy children with a BMI < 23 kg/m^2 was assessed by estimation of confidence interval (CI), which was 0.95 (–1.73–0.08).

In our own research, using the Waldo-Wolfowitz test we established the statistical validity of differences between ill children (IA + IB) and healthy children, considering the LEP random variable per BMI unit, with the assumed validity level of α, p = 0.01. The assessed groups differed from each other in LEP random variable per BMI unit, not only on expected medians, but also on probability distribution form, e.g. random variable value diversification.

Discussion

There is very little information available in the literature about leptin concentrations in the serum of children with JIA. The reported data mainly focus on adults suffering from rheumatoid arthritis [16,21]. There is some data suggesting that LEP levels are lower in patients suffering from RA or JIA, as confirmed

Table I. *Statistical results for the assessed populations of children with juvenile idiopathic arthritis with a longer illness (IA), those with a shorter disease period (IB), and of healthy controls (IC)*

Tabela I. *Wyniki analizy statystycznej prób badanych populacji dzieci chorych na młodzieńcze idiopatyczne zapalenie stawów z długim (IA) i krótkim (IB) czasem trwania choroby oraz u dzieci grupy kontrolnej (IC)*

Statistical Feature	n	Mean	Me	Min	Max	IQR	SD	SEM	As	SEAs
LEP-IA [ng/cm^3]	22		5.85	1.24	37.5	7.74			2.24	0.64
LEP-IB [ng/cm^3]	20		2.46	0.93	40.1	2.47			1.83	0.69
LEP (IA+IB) BMI < 23 [kg/m^2]	28	2.01		0.93	3.63		0.98	0.35	0.48	0.75
LEP-IC [ng/cm^3]	28		2.85	2.4	3.74	0.65			0.84	0.75
WBC-IA [G/L]	22		7.7	41	13.6	2.65			0.5	0.64
WBC-IB [G/L]	20		8.75	4.90	14.8	4.5			0.75	0.69
WBC-IC [G/L]	28		7.4	5.4	7.5	1.95			–0.64	0.75
LYMPH-IA (%)	22	39.13		16.8	61.6		12.57	3.63	0.21	0.64
LYMPH-IB (%)	20	35.39		12.7	63.9		14.87	4.7	0.42	0.69
LYMPH-IC (%)	28		7.4	5.4	7.5	1.95			–0.64	0.75
HBG-IA [g/dL]	22	12.13		9.4	15.1		1.41	0.41	0.26	0.64
HBG-IB [g/dL]	20	12.42		10.4	14.2		1.13	0.36	–0.29	0.69
HBG-IC [g/dL]	28		12.9	12.4	13.9	0.45			1.3	0.75
HCT-IA (%)	22	38.87		30.8	47.4		4.04	1.17	0.2	0.64
HCT-IB (%)	20	39.57		33.4	45.9		3.52	1.11	0.03	0.69
HCT-IC (%)	28		39	37	43	2			0.64	0.75
ESR-IA [mm/h]	22		12.5	4	40	12			1.12	0.64
ESR-IB [mm/h]	20	13		4	25		7.9	2.5	0.3	0.69
ESR-IC [mm/h]	28		2.5	1	5	2.35			0.53	0.75
BMI-IA [kg/m^2]	22	16.61		13.32	21.28		2.45	0.71	0.48	0.64
LEP/BMI-IA	22		0.33	0.09	1.76	0.59			1.49	0.64
BMI-IB [kg/m^2]	20		15.89	13.82	29.94	4.95			1.48	0.69
LEP/BMI-IB	20		0.15	0.06	1.54	0.19			1.90	0.69
BMI-IC [kg/m^2]	28	1.,91		17.16	20.41		0.95	0.34	–0.42	0.75
LEP/BMI-IC	28	0.15		0.13	0.20		0.03	0.01	0.47	0.75
Age-IA (years)	22	13.08		7	18		3.26	0.94	–0.39	0.64
Age-IB (years)	20	9.7		4	17		4.22	1.33	0.38	0.69
Age-IC (years)	28	11.25		8	15		2.82	1	0.02	0.75
Time Dis.-IA (months)	22		82	51	148	62			0.50	0.64
Time Dis.-IB (months)	20		8	2	18	7			2.23	0.69

N — sample size; Mean — arithmetic mean; Me — median; IQR — interquartile range; SD — standard deviation; SEM — standard error of the arithmetic mean; As — coefficient of unbalance (skewness); SEAs — asymmetry coefficient standard error; Min — minimum value in the studied statistical sample; Max — maximum value in the studied statistical sample

by the Perfetto et al. research team which assessed LEP levels in children suffering from JIA [17], whereas Nishiya et al. and Anders et al. did not find any significant differences between LEP levels of healthy patients and patients suffering from RA [18, 22]. Our research has indicated the presence of ANA antinuclear antibodies in 58.3% of children with long-term JIA, as well for 50% of children with short-term disease, whereas there was no presence detected in the control group. The relation between the tested disease and level of LYMPH and ESR level has been determined. The ill children proved to have higher LYMPH and ESR with much higher diversification of both, in comparison with healthy children.

The presence of these antibodies indicates that JIA is an autoimmune illness. As the individual ANA subtypes and titre were not analysed, we cannot fully confirm their presence as a sign of any disease or its intensification.

In chronic inflammatory diseases like in rheumatoid arthritis, there is an increase in cytokine markers, including IL-1, IL-2, IL-6, IL-8, interferon γ, and TNF-α. These markers are responsible not only for inflammation during illness, but they can also may increase ob gene expression and, consequently, stimulate leptin synthesis. In patients with JIA, pro-inflammatory cytokines activity increases basal metabolic rates, which reduces body mass and causes gradual devastation [8,9]. Some research has demonstrated that starving patients suffering from JIA results in a decrease in disease activity, which is correlated with lower serum concentrations of leptin; only considerable reduction of LEP stops disease progression. There are no unquestionable results concerning LEP for patients with chronic connective tissue illnesses [7, 26]; there has been, however, speculation that leptin is involved in connective tissue systemic diseases.

The tests carried out in this work confirm that leptin modulates the inflammatory process in juvenile idiopathic arthritis by causing various inflammatory mechanisms; however, the literature shows that the role of leptin in JIA has not yet been completely clarified and requires more precise research on the subject.

The results of this study helped to formulate following conclusions:

Conclusions

1. Children with juvenile idiopathic arthritis with BMI < 23 kg/m^2 had lower leptin concentrations in comparison with healthy subjects.
2. Ill children with a shorter-term disease had a higher diversification of leptin concentration per BMI unit than the healthy controls.

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