Relationship between insulin-like growth factors (IGF-I and IGF-II), IGF-binding proteins (IGFBP-3, IGFBP-2), leptin and anthropometric parameters (height, body mass index) during antileukaemic treatment in children

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Abstract

Purpose: **The aim of the study was to estimate the anthropometric parameters and their relationship to serum levels of IGF-I, IGF-II, IGFBP-3, IGFBP-2 and leptin before and during intensive antineoplastic treatment for acute lymphoblastic leukaemia in children.**

Material and methods: **In 46 children in median age 6.6 years (range from 1.6 to 16) we evaluated at the time of diagnosis, after protocol I and after intensive treatment, height, body mass index (BMI) and IGF-I, IGF-II, IGFBP-3, IGFBP-2 and leptin.**

Results: **Height SDS lowered in successive points of analysis whereas BMI SDS rose after protocol II. IGF-I SDS was low and similar at each point, IGF-II SDS and IGFBP-3 SDS values augmented progressively and IGFBP-2 SDS was significantly elevated before treatment and lowered (but not normalized) during the therapy. Leptin SDS was elevated, especially after protocol I.**

Conclusion: **leukaemia and its treatment affect directly growth factors, its binding proteins and leptin production leading to growth retardation and overweight.**

Key words: growth, body mass index, growth factors, leptin, acute lymphoblastic leukaemia, children.

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Introduction

Leukaemia and its composed treatment have severe catabolic effect especially on children, their development, growth and body composition. Corticosteroids and cytotoxic chemotherapy impair normal organ and tissues function such as liver, endocrine glands or cartillage growth plates [1]. Nutritional state and growth rest under influence of hormonal factors such as leptin and growth hormone (GH) which action is mediated by insulin-like growth factors (IGFs) and binding proteins (IGFBPs). Leptin, produced by adipose tissue, plays an important role in regulation of energy intake, expenditure and consequently – in regulation of body composition [2,3]. The importance of hormonal factors (mentioned above) is well known during normal development, growth and puberty in healthy children. In the present study we evaluated the relation between IGF-I, IGF-II, their binding proteins, leptin values and anthropometric parameters in children with newly diagnosed acute lymphoblastic leukaemia (ALL) and during intensive anticancer therapy.

Material and methods

Forty-six children (32 boys) in median age 6.58 years (range from 1.56 to 16.0) with newly diagnosed ALL (42-preB ALL, 4-T-ALL) were included in our study. All patients were treated according to ALLIC/BFM 2002 protocol.

The analysis was made:

1. at the time of diagnosis,
2. after protocol I (induction remission consisting prednisolone 60 mg/m^2 for 28 days, vincristine, asparaginase, cyclophosphamide, daunorubicine, cytarabine, adriamycine, 6-mercaptopurine and methotrexate – ith.), together 64 days,
3. after the end of intensive treatment; that is after protocol M including 6-mercaptopurine, methotrexate (iv. and ith.) and protocol II – with dexamethasone 10 mg/m^2 for 22 days, vincristine, doxorubicine, asparaginase, cyclophosphamide, cytarabine, 6-thioguanine).

Table 1. **Mean (±SEM) SDScore values for auxological and biochemical parameters in analysed points of ALL treatment**

	Height (SDS) N=46	BMI (SDS) N=46	IGF-I (SDS) N=46	IGF-II (SDS) N=46	IGFBP-3 (SDS) N=46	IGFBP-2 (SDS) N=46	Leptin (SDS) N=46	IGFBP-2: IGF-I N=46	Leptin: BMI N= 46
At diagnosis	0.54±1.7	-0.42±2.0	-1.71±0.9	-0.01±1.5	-0.27±2.3	10.96±8.5	2.12±1.5	28.39±21.0	0.30±0.3
After Protocol I	0.15±1.5	-0.39±2.4	-1.86±1.3	0.64±1.4	0.92±1.9	10.74±7.5	3.13±3.3	17.27±11.8	0.28±0.2
After Protocol II	-0.36±1.0	0.2±2.1.0	-1.8±0.9	0.83±2.0	1.75±2.4	8.03±7.3	2.88±3.1	12.49±11.7	0.52±1.3

All intensive treatment (protocols I, M, II) lasted on six months.

We measured at each time-point: height, weight, body mass index (BMI) – calculated as weight (kg) divided by the square of height (m^2) and biochemical parameters.

The samples were obtained after overnight fast and the serum was stored at -70°C until the analysis. Using radioimmunoassay methods, we determined the serum concentration of IGF-I (Source kit), IGF-II (DSL kit), IGF BP-3 (DSL kit), IGF BP-2 (OBRA-Polatom kit) and leptin (Linco HL-81 kit).

All data were presented as SDScore according to age and sex using Polish reference values for height and BMI [4]. The values of IGF-I, IGF-II, IGFBP-2, IGFBP-3 and leptin were compared to those obtained by Blum et al. and Juul et al. [2,3].

The study was approved by the Local Ethics Commitee.

Statistical analysis was performed using Statistica 5.0 for Windows. Results are showed as mean and standard deviation for normally distributed values and median significance levels were calculated according to the nonparametric Wilcoxon test. The Spearman correlation coefficient was also used. A level of $p<0.05$ was regarded as significant.

Results

All data of auxological values and biochemical parameters (as SDScore) are presented in *Tab.1*.

1. Auxological values: The mean height SDS at diagnosis (H1SDS) was 0.54±1.73 and lowered after protocol I (H2SDS) to 0.15±1.5 and to -0.36±1.04 after the end of intensive treatment (H3SDS) – $p<0.008$ between H1SDS and H3SDS and $p<0.005$ between H2SDS and H3SDS.

The mean BMI SDS did not differ at the time of diagnosis (-0.42±1.99) and after protocol I (-0.39±2.42) but rose after protocol II (0.20±2.10 ($p<0.05$ between BMI 2 SDS and BMI 3 SDS).

2. Biochemical parameters: IGF-I SDS was similar at diagnosis (-1.71±0.86), after protocol I (-1.86±1.35) and after protocol II (-1.8±0.89). IGF-II SDS augmented after each point of analysis: it was at the beginning -0.01±1.5, after protocol I – 0.64±1.39 ($p<0.001$), after protocol II – 0.83±2.01 ($p<0.0006$ between first and third point of analysis). IGFBP-3 SDS rose from -0.27±2.27 at diagnosis to 0.92±1.95 after protocol I ($p<0.006$) and to 1.75±2.42 after protocol II ($p<0.00007$ between first and third point of analysis and $p<0.03$ between second and third point). IGFBP-2 SDS was significantly elevated in all moments of analysis but lowered gradually from 10.96±8.46 (at diagnosis) to 10.74±7.47 (after protocol I) and to 8.03±7.32 (after protocol II); $p<0.05$ between values at diagnosis and the end of treatment.

The values of leptin SDS was higher after protocol I (3.13±3.3) comparing with the time of diagnosis (2.12±1.54) ($p<0.01$) and – with the end of intensive treatment (2.88±3.08).

The ratio of IGFBP-2: IGF-I was highest at diagnosis (28.39±21.05), lowered after protocol I (17.27±11.84, $p<0.006$) and after protocol II (12.49±11.75, $p<0.007$). The ratio of leptin: BMI did not change during the time of observation – at diagnosis it was 0.30±0.28, after protocol I – 0.28±0.25 and after protocol II – 0.52±1.29.

3. At the time of diagnosis we found a positive correlations between: a) height and: IGF-I ($r=0.75$, $p<0.001$) and IGFBP-3 ($r=0.485$, $p<0.01$) b) BMI and: leptin ($r=0.44$, $p<0.003$), IGF-I ($r=0.53$, $p<0.0003$), IGFBP-3 ($r= 0.68$, $p< 0.001$).

After protocol I we observed a positive correlation between a) height and IGF-I ($r=0.79$, $p< 0.0001$), IGFBP-3 ($r=0.45$, $p<0.01$) and leptin ($r=0.40$, $p<0.03$), b) BMI and: leptin ($r=0.59$, $p<0.001$) and IGFBP-3 ($r=0.49$, $p<0.02$).

After the end of intensive treatment we found the positive correlations between a) height and: IGF-I ($r=0.57$, $p<0.001$), IGFBP-3 ($r=0.53$, $p<0.002$), IGF-II ($r=0.48$, $p<0.008$), leptin ($r=0.32$, $p<0.05$) b) BMI and IGF-I ($r=0.55$, $p<0.008$), IGFBP-3 ($r=0.69$, $p<0.0001$), IGF-II ($r=0.53$, $p<0.02$) and – c) negative correlation between BMI and IGF BP-2 ($r=-0.32$, $p<0.05$).

We also observed the following correlations: at the time of diagnosis – a positive correlation between IGF-I and IGFBP-3 ($r=0.60$, $p<0.002$), IGF-I and leptin ($r=0.67$, $p<0.001$), IGF-I and IGF-II ($r=0.44$, $p<0.004$), IGF-II and IGFBP-3 ($r=0.57$, $p<0.0001$) and negative correlation between IGF BP-2 and: IGF-II ($r=-0.40$, $p<0.02$) and IGF-I ($r=-0.65$, $p<0.001$). After protocol I we found a positive correlation between IGF-I and leptin ($r= 0.73$, $p<0.0001$), IGF-I and IGFBP-3 ($r=0.63$, $p<0.002$), IGF-II and IGFBP-3 ($r=0.37$, $p<0,03$), IGFBP-3 and leptin ($r=0.53$, $p<0.001$) and after protocol II: a positive correlation between IGF-I and IGFBP-3 ($r=0.75$, $p<0.0001$), IGF-II and IGFBP-3 ($r=0.82$, $p<0.0001$), IGF-I and IGF-II ($r=0.52$, $p<0.02$) (*Tab. 2*).

Discussion

We made the simultaneous analysis of growth, body mass index and serum insulin-like growth factors, its binding proteins

Table 2. **Correlations between auxological and biochemical parameters expressed as absolute values: I – at diagnosis, II – after protocol I, III – after protocol II**

I

IGF-II	r=0.44 p=0.004					
IGFBP-3	r=0.60 p<0.002	r=0.57 p<0.001				
IGFBP-2	r=-0.65 p<0.001	R=-0.4 P<0.02	r=-0.24 p=0.13			
Leptin	r=0.67 p<0.001	r=0.23 p=0.3	r=0.22 p=0.16	r=-0.28 p=0.08		
Height	r=0.75 p<0.001	r=0.41 p=0.05	r=0.49 p<0.01	r=-0.36 p=0.02	r=0.13 p=0.39	
BMI	r=0.53 p=0.0003	r=0.22 p=0.32	r=0.68 p=0.001	r=-0.11 p=0.63	r=0.44 p<0.003	r=0.49 p=0.02
	IGF-I	**IGF-II**	**IGFBP-3**	**IGFBP-2**	**Leptin**	**height**

II

IGF-II	r=0.35 p=0.12					
IGFBP-3	r=0.63 p<0.002	r=0.37 p=0.003				
IGFBP-2	r=-0.9 p=0.67	r=0.04 p=0.82	r=0.14 p=0.44			
Leptin	r=0.73 p=0.0001	r=-0.0002 p=0.98	r=0.53 p=0.001	r=-0.12 p=0.6		
Height	r=0.79 p=0.0001	r=0.31 p=0.09	r=0.45 p<0.01	r=-0.01 p=0.93	r=0.4 p=0.03	
BMI	r=0.43 p=0.053	r=0,09 p=0.63	r=0,49 p<0.02	r=0.12 p=0.53	r=0.59 p=0.001	r=0.04 p=0.8
	IGF-I	**IGF-II**	**IGFBP-3**	**IGFBP-2**	**Leptin**	**height**

III

IGF-II	r=0.52 p=0.02					
IGFBP-3	r=0.75 p=0.0001	r=0.82 p=0.0001				
IGFBP-2	r=-0.24 p=0.15	r=0.003 p=0.99	r=-0.20 p=0.38			
Leptin	r=0.17 p=0.45	r=0.19 p=0.39	r=0.8 p=0.12	r=-0.18 p=0.42		
Height	r=0.57 p=0.001	r=0.48 p<0.008	r=0.53 p<0.002	r=-0.27 p=0.15	r=0.32 p=0.05	
BMI	r=0.55 p=0.008	r=0.53 p=0.02	r=0.69 p=0.0001	r=-0.32 p=0.05	r=0.29 p=0.19	r=0.39 p=0.03
	IGF-I	**IGF-II**	**IGFBP-3**	**IGFBP-2**	**Leptin**	**height**

and leptin during intensive treatment for ALL. In our previous study we demonstrated normal height and weight values in children and adolescent treated with chemotherapy alone or additionally received 12Gy for central nervous system [5]. The actual study made during the intensive treatment showed the tendency to decline growth velocity at the following point of analysis. BMI SDS values did not change after protocol I (with prednisolone) but increased after protocol II (with dexamethasone). This confirms the observations made by Wallace et al. [6] who proved that dexamethasone leads to greater change in BMI than prednisolone during induction chemotherapy for ALL.

The prospective study of Ahmed et al. [7] during intensive treatment for ALL showed a decline of height SDS at the beginning of treatment with a nadir at 6 month of chemotherapy with the increase of weight SDS and BMI SDS.

The longitudinal studies made during and after chemotherapy suggest that linear growth is most affected during intensive and maintenance therapy and followed by "catch-up" after the end of treatment. The tendency to overweight was affirmed by many investigators not only during the treatment, but also after the termination of therapy [1,8,9]. This weight gain is due to excessive fatness. Increased whole body percent of fat was observed even in patients with normal body mass index, what it was confirmed by Dalton et al. and in our previous study [8,10].

The patogenesis of developmental disturbances is multifactorial including malignancy per se, intensive chemotherapy and especially – corticotherapy and radiotherapy for CNS, reduced physical activity. The disturbances in the GH-IGF axis, impaired production of IGFs and its binding proteins by the liver are responsible for those problems [8,9]. Our observations indicated lowered values of IGF-I SDS accompanied by the increase of IGF-II SDS (from –0.01 to 0.83) and IGFBP-3 SDS (from -0.27 to 1.75).

IGFBP-2 production was most affected. We noted significantly elevated IGFBP-2 SDS values at the time of diagnosis (10.96±8.5) which lowered (but did not normalise) at the termination of intensive treatment (8.03±7.3). Similar tendency was observed by Mohnike et al. [11] who suggested the involvement of IGF system, especially IGFBP-2, in the proliferation of leukaemic cell clones. On the other hand IGFBP-2 levels are higher in other pathological situations such as growth hormone deficiency, hyponutrition which often accompany leukaemia and its treatment [12]. We found considerably elevated values of IGFBP-2: IGF-I ratio, especially at diagnosis, which lowered but rested high during all observation. Similar situation was recorded 6 months after diagnosis by Arguelles et al. [13] and Barrios et al. [12] and in their opinion it is a sign of catabolic state. The autors suggest partial and transient GH insensitivity provoked by leukaemia per se and its aggressive treatment what may explain the growth retardation in those patients. According to Brennan et al. [14], reduced IGF-I SDS values in children with malignancies are a sign of nutritional status, whereas normal IGFBP-3 values result from increased activity of IGFBP-3 protease.

Attard-Montallo et al. [15] in the study concerning different malignancies showed normal IGF-I and IGFBP-3 levels before and after intensive chemotherapy with the decrease at the time of febrile neutropenia. In their opinion these catabolic episodes provoke GH resistance.

We observed at diagnosis a positive correlation between IGF-I, IGF-II and IGFBP-3 and negative – between IGFBP-2 and IGF-I and IGF-II. During and after intensive treatment the similar correlations between IGF-I, IGF-II and IGFBP-3 and lack of correlations with IGFBP-2 were found. The similar results obtained by Mohnike et al. [11] suggest the different

regulation of IGFBP-2 and IGFBP-3 and the importance of IGFBP-2 in lymphoblasts proliferation.

In our group the leptin SDScore was increased at each point of observation, with its highest level after protocol I. Hyperleptinaemia was observed by Davies et al. [16] and Arguelles et al. [9] not only during intensive treatment for ALL but also increased after its cessation, suggesting a leptin resistance. We did not observe differences in leptin: BMI ratio although this values progressively augmented. Wallace et al. [6] found the increase of leptin: BMI ratio between fourth and sixth week of treatment with the decrease in following weeks. They suggest that increase in fat mass with leptin resistance is due to corticotherapy and the direct effect of glucocorticoids on adipocytes.

We noted a positive correlations between leptin and IGF-I before treatment and after protocol I and between BMI and IGF-I, IGFBP-3 and leptin which affirm the role of growth factors and its binding proteins in weight gain.

Conclusions

Our study demonstrates that leukaemia and its intensive chemotherapy affect the production of growth factors, its binding proteins and leptin, which may be responsible for growth retardation and overweight.

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