CLINICAL STUDY

Anthropometric parameters and their relationship to serum growth hormone-binding protein and leptin levels in children with acute lymphoblastic leukemia: a prospective study

B Argüelles, V Barrios, M Buño, L Madero¹ and J Argente*Universidad Autónoma, Department of Pediatrics, Division of Pediatric Endocrinology and ¹Division of Pediatric Oncology, Hospital Universitario Niño Jesús, E-28009 Madrid, Spain**(Correspondence should be addressed to J Argente, Division of Pediatric Endocrinology, Hospital Niño Jesús, Avenida Menéndez Pelayo, 65, E-28009 Madrid, Spain; Email: argentefen@teleline.es)*

Abstract

Objective: The aim of this study was to follow auxological parameters and their relationship to serum growth hormone-binding protein (GHBP) and leptin levels in children with acute lymphoblastic leukemia (ALL).

Design and methods: In total, 26 prepubertal children with ALL were studied. We report these data at the time of the clinical diagnosis ($n = 26$) and at 6 ($n = 21$), 12 ($n = 21$), 18 ($n = 21$), 24 ($n = 20$), 30 ($n = 16$) and 36 months ($n = 16$) after beginning treatment.

Results: Serum GHBP levels decreased during the first 18 months and returned to normal when therapy was withdrawn. Height SDS increased at 24 months after diagnosis. Weight and the upper arm circumference had increased 6 months after chemotherapy withdrawal, whereas tricipital and subscapular skinfolds had increased both at 6 months after diagnosis and 6 months after therapy had stopped. Therefore, the tendency to become overweight is both an early and a late side-effect of anti-leukemia therapy. A significant positive correlation was found between serum leptin levels and every nutritional anthropometric parameter, with body mass index having the best relationship. However, serum GHBP levels were only correlated with BMI at the end of the study. No correlation was found between leptin and GHBP.

Conclusions: In children with ALL, linear growth is compromised during the acute phase of their illness and therapy; this is probably secondary to a state of partial and transient GH insensitivity. These patients tend to become obese after therapy withdrawal, with leptin being an excellent nutritional marker.

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of leukemia in children and accounts for one-quarter of all childhood cancers (1). Improved survival rates have resulted in increased attention being focused on late side-effects, which include recurring neoplasms, cardiotoxicity, neuropsychologic dysfunction and endocrinologic sequelae including growth impairment, precocious puberty, gonadal dysfunction and obesity (2–4).

Both leukemia and its treatment can have a severe catabolic effect on children. Even when well and in remission, children with cancer are severely catabolic (5) and consequently the growth hormone/insulin-like growth factor (GH–IGF) axis is altered. Situations of increased protein catabolism or net protein breakdown

result in insensitivity or resistance to GH, as reflected by reduced circulating levels of IGF-I and growth hormone-binding protein (GHBP) and growth failure. Furthermore, malnutrition, which often occurs in children with cancer, could contribute to these endocrine changes (6, 7).

The adverse effects of therapy on weight gain in children with ALL is, however, less well documented. Obesity is not only associated with elevated blood pressure, hyperlipidemia, altered glucose metabolism and cardiovascular disease, but also affects the psychosocial adaptation of long-term survivors (8, 9). Leptin, a product of the *ob* gene, regulates appetite and energy expenditure, but it may also have a more general role in the regulation of growth and sexual maturation (10). Several large studies in children have shown a strong correlation between serum leptin levels and adiposity

as determined by body mass index (BMI) (10–12). Furthermore, total deficiency in leptin or resistance to this protein can cause severe obesity (12).

The aims of the present study were: (i) to analyze the evolution of auxological data in ALL patients during 2 years of therapy and 1 year after treatment withdrawal; (ii) to determine the serum levels of GHBP and leptin in these children; and (iii) to study possible correlations between these parameters.

Subjects and methods

Subjects

The study population included 26 prepubertal children with ALL without central nervous system (CNS) involvement (19 males and 7 females) and 37 healthy age-matched children (24 males and 13 females). Diagnosis of ALL was made according to the definitions and requirements defined by the German cooperative group BFM (Berlin–Frankfurt–Münster) (13). The patients were studied at seven different points: at diagnosis ($n=26$), and at 6 ($n=21$), 12 ($n=21$), 18 ($n=21$), 24 ($n=20$), 30 ($n=16$) and 36 months ($n=16$) after the start of therapy. The distribution by risk groups was as follows: 11 standard-risk, 11 intermediate-risk and 4 high-risk. During the study period, 6 patients died (2 intermediate-risk and 4 high-risk). The therapy employed followed the BFM-90 protocol.

All normal subjects were referred to the Division of Endocrinology for suspected endocrine abnormalities and were found to be normal, each having a height and a BMI between -1 and 1 S.D. according to Spanish standards (14). This study has been approved by the Ethics Committee of the Hospital Niño Jesús.

The BFM-90 treatment schedule

Protocol I. This therapeutic phase was common for all risk groups. The duration was 64 days. The drugs used were prednisone, vincristine, daunorubicine, L-asparaginase, cyclophosphamide, arabinoside-C, 6-mercaptopurine and intrathecal methotrexate.

Protocol M. The duration was 56 days. The drugs used were 6-mercaptopurine, L-asparaginase, high-dose methotrexate and intrathecal methotrexate.

Protocol II. The duration was 49 days and the drugs employed included dexamethasone, vincristine, adriamidine, L-asparaginase, cyclophosphamide, arabinoside-C, 6-thioguanine and intrathecal methotrexate.

High-risk blocks. Therapeutic blocks 1, 2 and 3 lasted 6 days each. They were administered consecutively, with intervals of 15 days. They were repeated three times each.

Maintenance therapy. In this period, daily oral 6-mercaptopurine (50 mg/m^2) and weekly oral methotrexate

(20 mg/m^2) were used to complete 24 months from the beginning of the therapy.

Prophylactic cranial irradiation. Cranial irradiation was only administered to patients of the intermediate-risk and high-risk groups. This was applied in eight fractions delivered over two weeks to reach a total dose of 12 Gy.

Auxology At all study points we measured height, weight, BMI, tricipital skinfold (TS), subscapular skinfold (SS) and the upper arm circumference (UAC). The BMI was calculated as weight (kilograms)/height (meters)². The S.D. scores were based upon normative data from Spanish children (14).

Biochemical measurements

In all subjects, blood samples were drawn in conditions of fasting between 08.00 and 10.00 h. Serum leptin levels were determined by radioimmunoassay (Linco, Inc, St Charles, MO, USA). The intra- and interassay coefficients of variation were 4.2 and 7.8% respectively. Serum GHBP levels were determined in duplicate by a monoclonal assay (Endocrine Sciences, Calabasas Hills, CA, USA) by incubating patient serum with excess radiolabeled human GH (hGH) and the monoclonal antibody Mo Ab 263. The GH receptor binds to this antibody and to labeled hGH to form a trimolecular complex (anti-GH receptor/GHBP/¹²⁵I-hGH). The intra- and interassay coefficients of variation were 5.6 and 9.5% respectively.

Statistics

All data are reported as the mean $\pm$ S.E.M. Changes in the different parameters were assessed for seven periods, as follows: at diagnosis, and at 6, 12, 18, 24, 30 and 36 months after the start of therapy. The significance of these changes was analyzed by the Wilcoxon signed-rank test. Analyses were performed by one-way analysis of variance (ANOVA), followed by Scheffe's F test. Correlations were performed using simple regression analyses. $P < 0.05$ was chosen as the level of significance.

Results

Anthropometric parameters

There were no significant differences in anthropometric or biochemical parameters between the different treatment protocols. Hence, all data are reported together. The mean age at diagnosis for the 26 patients with ALL was 5.12 years (range: 1.66–10.0 years) and the mean age at the end of the study was 7.09 years (range: 5.5–9.0 years). The auxological data of patients with ALL at diagnosis and during the first 36 months of therapy are shown in Table 1. A significant increase in mean height S.D. at the end of therapy was found

Table 1 Auxological data SD scores (height, weight, TS, SS and UAC) in children with ALL over time.

Parameter	Time						
	Dx* n = 26	6 m† n = 21	12 m n = 21	18 m n = 21	24 m n = 20	30 m n = 16	36 m n = 16
Height							
Mean ± S.E.M.	0.55 ± 0.19	0.40 ± 0.19	0.71 ± 0.22	0.78 ± 0.20	0.97 ± 0.21	1.02 ± 0.22	1.03 ± 0.20
Range	−0.99–2.73	−0.96–1.9	−0.92–2.57	−0.77–2.18	−0.64–2.2	−0.64–2.68	−0.34–2.33
Weight							
Mean ± S.E.M.	0.79 ± 0.20	1.10 ± 0.24	0.86 ± 0.27	0.78 ± 0.26	1.26 ± 0.33	1.51 ± 0.26	1.50 ± 0.27
Range	−0.85–2.28	−0.15–2.27	−0.45–2.16	−0.45–1.8	0.21–3.28	0.49–3.76	0.82–3.32
TS							
Mean ± S.E.M.	0.34 ± 0.23	1.36 ± 0.38	0.78 ± 0.26	0.57 ± 0.23	1.04 ± 0.36	1.37 ± 0.24	1.78 ± 0.20
Range	−1.27–1.30	0.39–3.22	−0.23–2.71	−0.53–2.25	0.16–3.17	0.72–2.34	0.87–3.07
SS							
Mean ± S.E.M.	1.25 ± 0.39	1.90 ± 0.32	0.72 ± 0.33	0.86 ± 0.32	1.60 ± 0.45	1.88 ± 0.38	1.54 ± 0.28
Range	−0.92–3.44	0.82–4.00	−1.3–2.8	−0.58–2.93	0.13–3.96	0.42–3.6	0.87–2.73
UAC							
Mean ± S.E.M.	−0.30 ± 0.24	−0.18 ± 0.23	−0.27 ± 0.25	0.05 ± 0.28	0.40 ± 0.36	0.62 ± 0.15	0.97 ± 0.27
Range	−1.98–1.04	−1.43–1.70	−1.43–1.63	−1.23–1.89	−0.5–1.3	0.21–1.74	0.23–2.05

* Dx, at diagnosis; † m, months.

(Fig. 1A; ANOVA: $P < 0.05$). These patients had significantly increased skinfolds (tricipital and subscapular; ANOVA: $P < 0.05$) 6 months after diagnosis and 6 months after treatment suspension (Table 1; Fig. 1C and 1). However, weight and UAC only increased 6 months after chemotherapy withdrawal (Fig. 1B and 1; ANOVA: $P < 0.05$).

Biochemical results

Mean ± S.E.M. serum GHBP and leptin levels are expressed in Table 2. Serum GHBP levels (Fig. 2A) were significantly lower in patients with ALL at diagnosis compared with controls and did not change during the first 18 months, but returned to normal values 24 months after diagnosis (ANOVA: $P < 0.05$). Serum leptin levels (Fig. 2B) were significantly elevated in these patients 6 months after diagnosis and 1 year after chemotherapy withdrawal (ANOVA: $P < 0.05$).

There were no differences between boys and girls with regard to the different risk groups or the parameters analyzed at the time of diagnosis or during the study period.

Regression analyses

The results of all regression analyses performed are represented in Table 3. A significant positive correlation was found between serum leptin levels and every nutritional anthropometric parameter (weight, BMI, TSs, SSs and UAC), with BMI having the best relationship (Fig. 3). Serum GHBP levels correlated significantly with weight and BMI only at the end of the study. Serum GHBP levels correlated with height at various

times throughout the study, with the strongest correlation occurring after 1 year without therapy. No correlation was found between GHBP and leptin.

Discussion

Acute lymphoblastic leukemia is the most frequent childhood malignancy (1). Because of the increasing number of long-term survivors in recent decades, it is important to determine the late side-effects of this disease and its treatment, including growth failure and obesity. In the present study we report auxological data and serum levels of GHBP and leptin in a group of prepubertal children with ALL at the time of clinical diagnosis and at 6, 12, 18, 24, 30 and 36 months after the start of therapy. As this is the first reported study in which these parameters have been measured simultaneously in the same population at seven stages of disease evolution, we also analyzed the correlations between these variables.

Growth retardation is a common finding in children successfully treated for ALL. Various factors have been cited as contributing to this growth retardation, including the catabolic state due to the disease itself, infections, reduced energy intake, chemotherapy and cranial irradiation (15). Unfortunately, the data on growth after therapy for childhood acute lymphoblastic leukemia are conflicting. It is well known that cranial radiotherapy may produce GH deficiency (16, 17); however, the effect of the illness itself and the chemotherapy on linear growth is less well understood. Both leukemia and its treatment can have severe catabolic effects in children. Even when well and in remission, children with cancer are severely catabolic,

Figure 1 Mean (± S.E.M.) SD score for height (A), weight (B), TS (C), SS (D) and UAC (E) of patients with ALL from diagnosis until 3 years after diagnosis (*ANOVA, $P < 0.05$).

as indicated by an increase in protein breakdown and, to a lesser degree, protein synthesis (5). In conditions that have malnutrition and net protein catabolism in common, a GH-resistant state is often present (6).

The growth-promoting and metabolic actions of GH are mediated by specific GH receptors (GHRs) on the surface of target cells. The absence of or reduction in functional GHRs results in GH insensitivity and growth

Table 2 Mean ± S.E.M. serum values for GHBP (pmol/l) and leptin (ng/ml) in controls (C) and patients with ALL over time. Abbreviations are as given in Table 1.

Parameter	C n=37	Dx n=26	6m n=21	12m n=21	18m n=21	24m n=20	30m n=16	36m n=16
GHBP	1166 ± 65	720 ± 72	912 ± 72	962 ± 84	927 ± 76	1056 ± 79	1222 ± 58	1108 ± 98
Leptin	5.1 ± 0.5	6.2 ± 1.2	8.8 ± 1.4	5.6 ± 1.2	5.7 ± 0.9	6.0 ± 1.2	5.6 ± 0.7	10.1 ± 0.7

Figure 2 Schematic representation of the mean $\pm$ S.E.M. serum levels of GHBP (A) and leptin (B) in controls (C) and in patients with ALL over time (*ANOVA, $P < 0.05$).

failure (18). It is difficult to study GHR abundance and function directly in humans; however, several observations indicate a direct relationship between GHBP and GHR levels. Both GHBP and the GHR are products of the GHR gene (10).

Our data support previous observations that linear growth is compromised during initial chemotherapy but is then followed by 'catch-up' growth (19, 20). Such gains became significant by the 24th month of

therapy. We cannot establish the exact cause of the decrease in growth rate during the initial treatment period, but chemotherapy must be important in this respect. 'Catch-up' growth occurred during maintenance therapy, when the treatment was less aggressive than in the first therapeutic phase. In our study, no difference was detected between irradiated and non-irradiated children during the 3 years after diagnosis; this suggests that cranial irradiation, at a dose of 12 Gy, does not play a major role in modulating height SD scores.

The results of the present study are consistent with those of previous reports (21) and demonstrate clearly that, at diagnosis, serum GHBP levels in ALL patients are significantly lower than control values. This is comparable to that which is observed in malnutrition and other catabolic conditions such as trauma, sepsis, surgery and organ failure (6). Serum GHBP levels were low during the first 18 months and then returned to normal values when therapy was withdrawn. Furthermore, serum IGF-I levels were significantly reduced until 1 year after therapy withdrawal and growth velocity increased significantly during the same period (22). This partial and transient GH insensitivity, as suggested by the low GHBP and IGF-I levels, induced by the acute phase of illness and therapy may explain the growth retardation observed in these patients. This possible state of GH-resistance must play an important role, as 'catch-up' growth does not occur until GHBP levels are normalized. Indeed, at the end of study there was a very strong correlation between GHBP and height.

Some investigators have reported that body composition plays a key role in the regulation of GHBP levels, there being a positive correlation between serum GHBP levels and BMI in healthy children and adults (23). However, we did not find this correlation in patients with anorexia nervosa (24), an extreme catabolic state. In the present study of children with ALL, serum GHBP

Table 3 Linear correlation ($P < 0.05$) between GHBP and leptin and the nutritional anthropometric parameters studied (height, weight, BMI, TS, SS and UAC) at diagnosis, and at 6, 24 and 36 months after the start of therapy.

Parameter	Height	Weight	BMI	TS	SS	UAC
At diagnosis						
GHBP	0.36	0.32	NS*	NS	NS	NS
Leptin	NS	0.42	0.59	0.49	0.26	0.57
At 6 months						
GHBP	NS	NS	NS	NS	NS	NS
Leptin	NS	0.64	0.72	0.64	0.63	0.78
At 24 months						
GHBP	0.41	NS	NS	NS	NS	NS
Leptin	NS	0.81	0.91	0.73	0.84	0.75
At 36 months						
GHBP	0.97	0.72	0.44	NS	NS	NS
Leptin	NS	0.77	0.82	0.58	0.71	0.60

*NS, not significant.

Figure 3 Linear correlation between BMI and serum leptin levels in children with ALL at diagnosis (A), 6 (B), 24 (C) and 36 months (D) after the start of therapy.

levels showed a strong correlation with BMI, which is similar to the situation in normal subjects.

The children in our study had a tendency to gain weight after the termination of therapy. The frequency and pattern of obesity in survivors of ALL is less well documented than the effect of this disease on linear growth. Nevertheless, it is calculated that nearly half of the long-term survivors of childhood leukemia are overweight (25, 26). Endocrine disorders causing blunted growth, e.g. hypothyroidism, hypercortisolism and GH deficiency, are often associated with obesity (27). However, in ALL patients the etiology is almost certainly multifactorial. Factors such as cranial irradiation, chemotherapy, treatment with corticosteroids, lack of physical exercise and poor dietary habits probably contribute to the excess weight gain in these patients (26). Cranial irradiation may cause damage to the hypothalamic–pituitary axis, affecting the secretion of GH and inducing a neurosecretory dysfunction, resulting in a decrease in growth and lipolysis and possibly obesity (8, 27). Excess weight gain during and after treatment for leukemia is also seen in children treated only with cytotoxic drugs and corticosteroids. Several investigators have shown that the use of corticosteroid therapy, especially with dexametasone, has an important effect on weight (8, 27, 28).

In the present study, evolution of the nutritional anthropometric parameters varied. Weight and UAC only increased 6 months after chemotherapy withdrawal,

whereas TSs and SSs were increased both at 6 months after diagnosis, when height was significantly reduced, and at 6 months after therapy was stopped. Corticosteroids, which were used in the first 6 months after diagnosis, could explain the rise in the TSs and SSs. Therefore, the increase in weight observed during and after chemotherapy withdrawal in the present study and by others (4, 26) suggests an effect of chemotherapy on body composition, although the mechanism is unknown.

We confirm previous data (8, 27) showing no difference between irradiated and non-irradiated children or between boys and girls during the 3 years after diagnosis. This suggests that neither cranial irradiation at a dose of 12 Gy nor gender plays a major role in body-weight evolution in these patients. This is in contrast to the data of Odame *et al.* (4), who conclude that obesity in patients treated for ALL is more pronounced in girls than in boys, and that cranial irradiation is an important factor. However, it will be some time before sufficient data can be accrued to assess the effect of these regimens on adult body weight.

Leptin, which is produced in adipose tissue, acts as a hormonal feedback signal to regulate fat-cell size through hypothalamic mechanisms controlling food intake and metabolic rate (29–31). In normal pediatric subjects, leptin levels are highly correlated with the BMI, but this is not the case in patients with eating disorders where the BMI is either significantly elevated

or reduced (11). The fact that serum leptin levels are elevated in obese patients suggests a leptin resistance syndrome. Whether this is due to a reduction in leptin receptor number or responsivity or to a decrease in leptin bioactivity remains to be determined (12).

Recently it has been shown that cytokines, such as tumor-necrosis factor α (TNF α), can increase leptin levels and perhaps participate in loss of appetite and wasting in chronic disease (32). In our study, serum leptin levels were elevated in ALL patients 6 months after diagnosis and 1 year after chemotherapy withdrawal. The rise in serum leptin levels at 6 months after diagnosis could be secondary to the rise in body fat (as indicated by the increase in skinfolds) and the use of corticosteroids, which stimulate leptin synthesis (33). We found no differences in serum leptin levels between girls and boys or between irradiated and non-irradiated patients, whereas in Birkebaek's study, serum leptin was significantly higher in patients treated with cranial irradiation compared with the non-irradiated group (34).

A significant positive correlation was found between serum leptin levels and every anthropometric parameter (weight, BMI, TSs, SSs and UAC), with BMI having the strongest relationship. These findings are in agreement with the retrospective study of Birkebaek *et al.* (34). Furthermore, the correlation between leptin and GHBP that exists in normal subjects (10) is not found in prepubertal ALL children, suggesting an influence from other factors, such as cytokines, that are present in catabolic states (18, 32).

In summary, this study demonstrates that in prepubertal children with ALL, linear growth is compromised during the acute phase of illness and therapy. This is probably secondary to a state of partial and transient GH insensitivity, as indicated by low GHBP levels. Furthermore, catch-up growth occurs when GHBP levels normalize. These patients have a tendency to be overweight after therapy withdrawal and leptin seems to be an excellent nutritional marker as it shows good correlation with anthropometric parameters and was modified during those periods when changes in metabolism might be expected, i.e. at the beginning of treatment and upon its withdrawal.

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