Children With Idiopathic Short Stature Are Poor Eaters and Have Decreased Body Mass Index

Stefan A. Wudy*; Sandra Hagemann, MD*; Astrid Dempfle, PhD‡; Gundula Ringler, MSC‡; Werner F. Blum*§; Lars D. Berthold, MD∥; Gerhard Alzen∥; Ludwig Gortner∥; and Johannes Hebebrand#

ABSTRACT. Objective. In children with idiopathic short stature (ISS), studies investigating body mass index (BMI) or parameters of satiety regulation are scarce, and studies analyzing eating behavior are lacking.

Methods. We recruited 214 children (123 index cases and 91 siblings) with ISS from 123 families. Affected children had to have a body height <5th percentile, or, in the case of siblings, the body height of 1 child had to be <5th percentile and the other <15th percentile. Medical histories were recorded by using structured and standardized interviews. Eating behavior was assessed by using the Child Eating Behavior Questionnaire. Percent energy intake as fat was assessed by using the Leeds Food Frequency Questionnaire. Endocrine markers of body weight regulation (leptin, ghrelin) were determined in serum.

Results. Compared with population norms, BMI was significantly lower (mean: −0.33 standard deviation score). Furthermore, there was decreased food responsiveness (mean Child Eating Behavior Questionnaire score: 1.9; population mean: 2.4), reduced enjoyment of food (3.2 vs 3.9), emotional undereating (2.6 vs 3.0), lower desire to drink (2.0 vs 2.8), and increased fussiness over food (3.2 vs 2.9). When the sample was subdivided into the 2 groups of “good” and “poor” eaters according to the mothers’ assessment of the current eating behavior, reduction in BMI as well as the behavioral characteristics already delineated in the total sample were found to be even more consistent in the subgroup of poor eaters. In the total sample of our children, as well as in both subgroups, serum leptin (adjusted for gender, BMI, and Tanner stage) was found to be moderately raised but did not differ between poor and good eaters. Total serum ghrelin was not different between poor and good eaters.


ABBREVIATIONS. CDGP, constitutional delay of growth and puberty; FSS, familial short stature; ISS, idiopathic short stature; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor–binding protein 3; CEBQ, Child Eating Behavior Questionnaire; SDS, standard deviation score; LFFQ, Leeds Food Frequency Questionnaire.

Short stature is the most common cause for referrals to pediatric endocrinologists. Many of these patients have no identifiable medical abnormality and are classified with diagnoses such as constitutional delay of growth and puberty (CDGP), familial short stature (FSS), or idiopathic short stature (ISS). For most of these patients, the etiology of their short stature is currently unknown, although it is believed that genetic variations are the underlying cause.

In young children, CDGP is typically defined by short stature (height below the third age- and gender-specific percentile), bone-age retardation of at least 1 year, and a positive family history of delayed growth and pubertal development; however, in a strict sense, the diagnosis cannot be made before the time of puberty, when a delay in sexual maturation becomes evident. Patients with FSS reveal a family history of short stature, whereas osseous development and sexual maturation are appropriate for chronological age. In case both bone age and parental height are within the normal range (although often at the lower end), a diagnosis of ISS in its narrow meaning can be made. In clinical terms, however, these individual diagnostic categories often can not clearly be distinguished, resulting in combined diagnoses. We therefore chose to summarize all these subtypes under the general term and broader definition of ISS.

In a previous study from our hospital conducted between 2000 and 2002 (n = 220), 70% of patients with short stature were classified as ISS (wider meaning, see above), with 25% having CDGP, 7% having FSS, 30% having a combination of CDGP and FSS, and 8% having ISS in the narrow meaning. The large overlap between CDGP and FSS points to a close relationship between these conditions. It has already been hypothesized that CDGP and FSS are likely to present either a single population with a continuum of skeletal age delay and parental stature or 2 largely overlapping populations. Pedigree anal-
ysis in patients with CDGP suggested strong familial aggregation.4 Many pediatric endocrinologists have conceived the impression from their daily routine that children with CDGP as well as those with FSS or ISS tend to be lean5–6 and are often characterized as poor and fussy eaters by their parents. Most research has concentrated on aspects such as final height7 or adjuvant therapy.8,9 With the exception of a single study of prepubertal children with ISS,10 in which significantly lower body mass index (BMI) values were found, data regarding systematic characterization of BMI and eating behavior are lacking. This is surprising, because suboptimal nutrition in childhood has been suggested to contribute to the onset and persistence of failure to thrive.11 Therefore, it was our aim in the present study to systematically delineate eating behavior, BMI, and endocrine parameters of body weight regulation.

SUBJECTS AND METHODS

Study Population

All children who presented between November 2001 and August 2003 at the endocrine outpatient clinic of the Children’s University Hospital of Giessen (Giessen, Germany) and were diagnosed as having ISS served as index patients and were prospectively enrolled in our study. The term “ISS” is used in this report as the overarching diagnosis, indicating that the etiology of short stature in these patients was unknown. It included patients who were diagnosed as CDGP, FSS, or a combination of both; however, it excluded patients who were born short for gestational age. Additional index cases were recruited retrospectively from our hospital database and comprised children with ISS who had attended our endocrine outpatient clinic between 1996 and 2001. The families of the index cases were contacted by phone, and the whole family was invited to participate in the study, which was conducted in our clinical endocrine research unit. In total, 214 children with ISS from 123 families were recruited for the investigation, including 123 index cases and 91 siblings. The study protocol was approved by the ethics committee of the Justus Liebig University of Giessen, and written informed consent was obtained from the parents.

Inclusion Criteria

To be included in the study, patients had to have a body height <5th percentile,12 or, in the case of siblings, the body height of 1 child had to be <5th and the other <15th percentile. Only white and nonconsanguineous families were considered. The gestational history had to be uneventful and birth weight had to be >3rd percentile for gestational age.13 Children with dysmorphic features or chronic diseases were excluded; this was ensured by tests for chronic inflammatory (erythrocyte sedimentation rate, blood count, C-reactive protein), celiac (gliadin and endomysium antibodies), hepatic (aspartate aminotransferase, alanine aminotransferase), or renal (creatinine) diseases and hypothyroidism (free thyroxin, thyrotropin). Growth-hormone deficiency was considered to be unlikely based on serum insulin-like growth factor I (IGF-I) and insulin-like growth factor–binding protein 3 (IGFBP-3) levels.

Data Collection

Medical histories of children and parents were recorded by using structured and standardized interviews. All interviews and clinical examinations were performed by the same physician (S.H.). Eating behavior was assessed by using the Child Eating Behavior Questionnaire14 (CEBQ), an instrument that allows the ascertainment of 8 dimensions of eating style developed in 400 British boys and girls. Daily energy and macronutrient intake was assessed according to the Leeds Food Frequency Questionnaire (LFFQ).15,16 Within a structured interview, we additionally asked mothers to characterize their children as “poor eaters” or “good eaters” by means of the following question: “Is or has your child been a poor eater? (ie, has your child ever eaten or drunk poorly for at least 4 weeks)” The options provided for answering this question were “yes,” “no,” “unknown,” or answer denied. Classification of the children as “poor” or “good” eaters was based on their current situation.

Body height was measured to the nearest 0.1 cm by using an Ulm Stadiometer (Busse, Ulm, Germany). A Söhne type 7723 digital portable scale (capacity of 250 kg, precision of 0.1 kg) was used for measuring body weight. Pubertal development was characterized according to Tanner stage (pubic hair and breast development in girls, testicular volume and genital development in boys). Body height and BMI (kg/m²) were compared with the most current German reference data from >34 000 children and adolescents.12 Target height was calculated according to Tanner et al.13 Bone age was assessed independently by 3 pediatric radiologists according to the method of Greulich and Pyle14 from radiograph films of the left hand. Bone-age determination was performed blinded for the patients’ birth date, and the mean of 3 readings for each radiograph was used. The interobserver agreement was very good as judged from pairwise Bland-Altman bias plots,15 in which mean differences between 2 raters were between 0.5 and 2.3 months and 95% limits of agreement were between 14 and 24 months. If available, radiograph films from earlier presentations at our outpatient clinic were considered as well (1–6 radiograph films were available per child), and the mean and maximal bone-age retardations at different time points were calculated.

IGF-I, IGFBP-3,20 leptin,21 and total ghrelin (Linco Research Inc, St Charles, MO) were measured in our endocrinologic laboratory. All other parameters were measured by routine methods in our hospital’s laboratory for clinical chemistry. For IGF-I and IGFBP-3, gender- and age-dependent standard deviation score (SDS) values were calculated,20 and leptin was transformed to SDS values according to gender, BMI, and pubertal stage.22

Data Analysis

Because our sample comprised both single children and pairs of siblings, not all observations were independent; consequently, group means considering all children would give incorrect estimates of underlying population means. Therefore, to calculate the appropriate means (as well as means for subgroups, eg, good and poor eaters) for different variables, we used a linear model (analysis of variance), which included family as an independent fixed factor (with subgroup as an independent random factor if applicable) and calculated marginal means over families. Using the same model, we also tested for differences between subgroups. LFFQ data were available only for 103 index patients (who are independent) and were compared between subgroups by using an unpaired t test. Data analysis was performed by using SPSS 11.0 (SPSS Inc, Chicago, IL).

RESULTS

Our sample of 214 children included 56 cases (26.2%) with a bone-age delay of >1 year, 43 cases (20.1%) of FSS, 92 cases (43.0%) with a combination of both conditions, and 23 cases (10.7%) without pronounced bone-age retardation and with normal target height. A summary of clinical and anthropometric data of the 123 index patients and 91 siblings is given in Table 1. With respect to gender distribution, there was a striking imbalance in the group of index patients, with a majority of almost two thirds being male gender, whereas no difference could be found among siblings. Additionally, body height was considerably lower, by almost 1 SDS, in index patients. Bone-age retardation was clearly more pronounced in index patients compared with their siblings. Between male and female siblings there was no difference in height SDS (mean height SDS in male siblings: −1.57; mean height SDS in female siblings: −1.52; P = .58).

Table 2 summarizes the data concerning the char-
aceterization of eating behavior in our patients with ISS. Initially, we compared the scores from the CEBQ with reference data from the literature. The complete group of patients showed a different behavior from the reference sample in some respects. In particular, our patients were characterized by decreased food responsiveness, reduced enjoyment of food, emotional undereating, lower desire to drink, and increased fussiness over food. When divided into the 2 groups of good and poor eaters, the behavioral characteristics, which were already delineated in the total sample, were found to be even more consistent in the subgroup of poor eaters. Poor eaters clearly revealed lower food responsiveness, higher satiety responsiveness, decreased enjoyment of food, and increased fussiness over food and were slower eaters. To complement the analysis of eating behavior as assessed by the CEBQ, we used the LFFQ to estimate mean daily energy intake and percent energy intake for fat, protein, and carbohydrates (Table 3). Good and poor eating behavior was not associated with significant differences in the amount or composition of energy intake as measured by this instrument. The mean BMI SDS of -0.33 in the whole sample corresponds to the 37th population percentile. Both good and poor eaters had mean BMI SDS values below the respective reference values, and the BMI SDS was significantly lower in the group of poor eaters. However, height differed significantly between the 2 subgroups: poor eaters had a markedly lower body height.

BMI SDS was not correlated significantly with chronological age. The mean BMI SDS was -0.36 for children with pronounced bone-age delay (>1 year), which was slightly lower than in the group of children with no or a slight delay (<1 year; mean BMI SDS: -0.16), but this difference was not statistically significant (P = .13).

In the overall group of children with ISS, serum concentrations of IGF-I were lower than population

| TABLE 1. Baseline Characteristics of Index Patients and Their Siblings Diagnosed With ISS |
|---------------------------------|-----------------|-----------------|
|                                | Index Patients (n = 123) | Siblings (n = 91) |
| Gender distribution, n (%)     | Males (76 [62%])       | Females (47 [38%]) |
|                                | females (45 [49%])     | males (46 [51%])  |
| Age, y, mean ± SD (range)      | 11.9 ± 3.6 (4.8 to 18.4) | 11.7 ± 4.2 (3.5 to 21.3) |
| Height, SDS, mean ± SD (range) | -2.3 ± 0.5 (-3.6 to -1.2) | -1.5 ± 0.5 (-3.3 to -1.1) |
| BMI, SDS, mean ± SD (range)    | -0.4 ± 0.8 (-2.1 to 2.5) | -0.1 ± 0.7 (-2.0 to 2.1) |
| Mean bone-age retardation, y, mean ± SD (range)* | -1.6 ± 0.9 (-3.6 to +0.5) | -0.8 ± 1.2 (-4.4 to +2.7) |
| Maximal bone-age retardation, y, mean ± SD (range)* | -1.9 ± 0.9 (-3.9 to +0.3) | -0.9 ± 1.2 (-5.5 to +2.7) |
| Mid parental height, cm, mean ± SD (range) | 167 ± 4 (157 to 178) |                     |

Bone-age retardation = bone age – chronological age.
* In case several radiograph films including those from earlier presentations were available, the respective means and maxima were calculated.

| TABLE 2. Eating Behavior and BMI of Index Patients and Siblings With ISS |
|---------------------------------|-----------------|-----------------|
| Item                            | Total Sample (n = 213) | Population Mean (Wardele et al14) |
|                                | Good Eaters (n = 122) | Poor Eaters (n = 91) |
| Food responsiveness             | 1.9               | 2.0               | 1.8               | .002 |
| Satiety responsiveness          | 3.0               | 3.0               | 2.6               | .33  |
| Fussiness of food               | 3.2               | 2.9               | 3.0               | .35  |
| Enjoyment of food               | 3.2               | 3.9               | 3.5               | .28  |
| Slowness in eating              | 2.9               | 2.8               | 2.6               | .31  |
| Emotional overeating            | 1.8               | 1.8               | 1.9               | .17  |
| Emotional undereating           | 2.6               | 3.0               | 2.5               | .27  |
| Desire to drink                 | 2.0               | 2.8               | 2.1               | .370 |
| BMI, SDS                        | -0.33             | -0.11             | -0.55             | .003 |
| Height, SDS                     | -2.06             | -1.81             | -2.31             | .001 |

The study sample was subdivided into good and poor eaters (see “Subjects and Methods”). Mean scores (marginal means over families) from the reference sample in some respects. In particular, our patients were characterized by decreased food responsiveness, reduced enjoyment of food, emotional undereating, lower desire to drink, and increased fussiness over food. When divided into the 2 groups of good and poor eaters, the behavioral characteristics, which were already delineated in the total sample, were found to be even more consistent in the subgroup of poor eaters. Poor eaters clearly revealed lower food responsiveness, higher satiety responsiveness, decreased enjoyment of food, and increased fussiness over food and were slower eaters. To complement the analysis of eating behavior as assessed by the CEBQ, we used the LFFQ to estimate mean daily energy intake and percent energy intake for fat, protein, and carbohydrates (Table 3). Good and poor eating behavior was not associated with significant differences in the amount or composition of energy intake as measured by this instrument. The mean BMI SDS of -0.33 in the whole sample corresponds to the 37th population percentile. Both good and poor eaters had mean BMI SDS values below the respective reference values, and the BMI SDS was significantly lower in the group of poor eaters. However, height differed significantly between the 2 subgroups: poor eaters had a markedly lower body height.

BMI SDS was not correlated significantly with chronological age. The mean BMI SDS was -0.36 for children with pronounced bone-age delay (>1 year), which was slightly lower than in the group of children with no or a slight delay (<1 year; mean BMI SDS: -0.16), but this difference was not statistically significant (P = .13).

In the overall group of children with ISS, serum concentrations of IGF-I were lower than population

| TABLE 3. Food Intake (From LFFQ) (n = 103 Index Patients) for the Sample and the Subgroups of Good and Poor Eaters |
|---------------------------------|-----------------|-----------------|
|                                | Total Sample (n = 103) | Good Eaters (n = 47) | Poor Eaters (n = 56) |
| Daily energy intake            | 8431             | 8314             | 8531             |
| % energy from fat              | 39.4             | 40.1             | 38.8             |
| % energy from protein          | 13.9             | 13.6             | 14.1             |
| % energy from carbohydrates    | 46.5             | 46.1             | 46.8             |

Differences between good and poor eaters were tested for statistical significance by using the t test.
norms (mean SDS: -1.0; \(P < .001\)) (Table 4), whereas serum concentrations of IGFBP-3 were somewhat higher (mean SDS: +0.3; \(P < .001\)). Leptin levels, adjusted for gender, BMI, and pubertal development, were significantly higher in the whole group than for population norms (mean SDS: +0.39; \(P < .001\)). Serum levels of ghrelin could not be compared with population data, because no reference values were available for the test kit. The differences between good and poor eaters were not significant for any of the endocrinologic parameters.

**DISCUSSION**

Our observation that short stature and bone-age delay were much more pronounced in the group of index patients than in the group of siblings reflects the fact that the more severely affected child in a family is generally the one presented to the pediatric outpatient clinic. The gender distribution among our index patients showed a higher percentage of boys compared with girls. In contrast, an equal gender distribution was found among the recruited siblings, suggesting that the frequency of short stature with or without developmental delay is similar between girls and boys. The preferential presentation of affected boys to the pediatric endocrinologist potentially suggests that parents are more concerned about the development of their sons than their daughters.

The CEBQ is a useful parent-rated measure of eating style for research on obesity or eating disorders. It allows the assessment of 8 dimensions of eating style in children. An overall comparison of our total sample of children with reference ranges in the literature\(^{14}\) revealed distinct differences in several aspects of eating. Responsiveness to food was clearly reduced in our patients, who did not seem to enjoy food as much as unaffected children; they had a reduced desire to drink and tended to eat less during negative emotional states. Additionally, our patients were somewhat more fussy (“picky”) eaters, in that they were highly selective about the range of foods accepted. All these altered parameters of eating behavior are in keeping with a specific behavioral pattern of eating style and, therefore, allowed characterization of this sample of children as poor eaters. Although this comparison was made with reference ranges from a British sample, the degree to which single dimensions of eating style were altered suggested that a truly distinct pattern of eating behavior existed in our patient sample.

We do not know how mothers of healthy children would rate their eating behavior. However, it was striking that, based solely on the mothers’ assessment, a high percentage of our patients had already been characterized as poor eaters. When we analyzed the eating behavior in this subgroup of poor eaters compared with the good eaters, we found that the aforementioned pattern of eating behavior was even more pronounced. Additionally, satiety responsiveness was found to be higher in the subgroup of poor eaters, and speed of eating was also reduced. The validity of the maternal assessment is substantiated further by the findings of lower BMI and height in the group of poor eaters. However, we are fully aware of the fact that, because of the lack of prospective data, these findings need to be interpreted with caution.

Considering the deviant eating behavior in our children with ISS, an important next question was whether, and by what mechanism, such an eating style had an impact on body weight. Indeed, we found moderately reduced BMI for the total sample of patients compared with German population norms, which again was more reduced in poor eaters. Thus, our data confirm the findings of Thibault et al,\(^{10}\) who examined prepubertal children with ISS (\(n = 79\)) and likewise found similarly reduced BMI values (BMI SDS: \(-0.4 \pm 0.1\)). Total energy intake and percent energy intake as fat did not differ between good and poor eaters. Percent energy intake as fat was similar to that observed for healthy German school children (unpublished data). However, the validity of food frequency questionnaires is debatable. Food frequency questionnaires cannot be used to reliably assess absolute energy intake.

It has been suggested that suboptimal nutrition in childhood can lead to impaired development of body height.\(^{23}\) Indeed, we found that poor eaters had a significantly lower height than the good eaters. Therefore, one could speculate that the poor eating behavior found in our patients might lead to suboptimal nutrition and could contribute to their short stature and developmental delay.\(^{11,24}\) On the other hand, it cannot be excluded that slow growth and development cause impaired drive for eating as long as energy stores are sufficiently replete. Therefore, the question of what comes first, reduced energy intake or slow growth, remains open.

The findings of an altered eating behavior and reduced BMI in children with ISS caused us to investigate further the role of 2 important regulators of satiety. Leptin, the product of the \(ob\) gene, is produced by adipocytes and acts on the hypothalamus, suppressing food intake and stimulating energy expenditure.\(^{25}\) Leptin reflects the proportion of body fat mass, its most important determining variable.\(^{21}\)
Furthermore, leptin seems to play a significant role in the initiation and progression of puberty.\textsuperscript{26} We calculated leptin SDS, adjusted for gender, BMI, and Tanner stage according to reference data (Fig 1).\textsuperscript{22} The total sample of our children, as well as both subgroups of good and poor eaters, revealed moderately raised serum leptin concentrations that were not significantly different between the subgroups. Among all children, we found that 13\% had a leptin SDS >1.96, compared with 5\% expected from a general population sample. It was unexpected that patients with ISS have relatively high leptin levels for their BMI, a fact that may indicate alterations in endocrine mechanisms of satiety regulation in parallel to the observed altered eating behavior. Furthermore, our results are not in accordance with observations made by other investigators in smaller samples of children. Gill et al\textsuperscript{28} studied 23 boys with CDGP and found lower BMI values only in prepubertal children, whereas leptin was decreased only in pubertal children. In contrast, Bideci et al\textsuperscript{26} assessed 80 children with CDGP and also found decreased BMI values and decreased serum levels of leptin, but they did not adjust leptin for BMI.

Ghrelin is a potent growth hormone secretagogue that exerts strong orexigenic effects. It has been shown to induce obesity in animals and stimulate appetite in humans.\textsuperscript{27} Increased levels of ghrelin in anorexia nervosa and weight loss, and reduced levels in obesity, have been reported.\textsuperscript{28,29} A comparison of the absolute ghrelin values of our study population with previously published data\textsuperscript{27,28} is not possible because different commercial assay kits provide different values. We used a new and recently developed approach to the measurement of total serum ghrelin; bioactive, octanoylated ghrelin could not be determined by our assay. Similar to leptin, total ghrelin did not show any differences between poor and good eaters.

CONCLUSIONS

Our clinical, behavioral, and endocrinologic findings in children with ISS point to an altered regulation of appetite and energy balance. It is possible that this altered regulation could contribute to the reduced height of these children. Alternatively, a currently unknown factor may induce both a reduced height growth and an altered eating behavior.

ACKNOWLEDGMENTS

This work was funded by German National Genome Research Network grant NGFN 01GO118 and the European Union (Diet and Obesity; grant QLK1-2000-00515).

We are grateful to the children and their parents for their participation in this study.

REFERENCES

4. Seidlmeyer IL, Palmert MR. Delayed puberty: analysis of a large case series from an academic center. J Clin Endocrinol Metab. 2002;87:1613–1620

Fig 1. Histogram of leptin SDS in the whole sample of ISS patients.
27. Haqq AM, Farooqi IS, O’Rahilly S, et al. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. J Clin Endocrinol Metab. 2003;88:174–178
Children With Idiopathic Short Stature Are Poor Eaters and Have Decreased Body Mass Index

Stefan A. Wudy, Sandra Hagemann, Astrid Dempfle, Gundula Ringler, Werner F. Blum, Lars D. Berthold, Gerhard Alzen, Ludwig Gortner and Johannes Hebebrand

Pediatrics 2005;116;e52
DOI: 10.1542/peds.2004-1684
Children With Idiopathic Short Stature Are Poor Eaters and Have Decreased Body Mass Index

Stefan A. Wudy, Sandra Hagemann, Astrid Dempfle, Gundula Ringler, Werner F. Blum, Lars D. Berthold, Gerhard Alzen, Ludwig Gortner and Johannes Hebebrand

Pediatrics 2005;116;e52
DOI: 10.1542/peds.2004-1684

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/116/1/e52.full.html