SHORT COMMUNICATION

Extremely low values of serum leptin in children with congenital generalized lipoatrophy

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Abstract

Congenital generalized lipoatrophy (CGL) is a syndrome with multiple clinical manifestations and complete atrophy of adipose tissue. The exact mechanism of this disease remains unknown. One hypothesis presupposes an abnormal development of adipocytes. Leptin, the adipocyte-specific product of the ob gene, acts as a regulatory factor of body weight. In children, as in adults, leptin levels are correlated with body mass index (BMI) and body fat mass. Some authors have demonstrated that adults with congenital or acquired generalized lipoatrophy have decreased leptin concentrations. In order to study serum leptin profile during childhood in this disease, we measured serum leptin concentrations in six children aged 5.5–11 years suffering from CGL, and investigated the relationship between metabolic parameters and the variations in leptin levels. Serum leptin concentrations (1.19 ± 0.32 ng/ml (± s.d.)) were extremely low compared with those observed in normal children. No significant correlation was found with BMI, which is known to be one of the major determinants of serum leptin. Serum leptin values were significantly correlated with fasting insulin levels (r = 0.83, P = 0.024). In conclusion, extremely low leptin values measured in children with CGL could be regarded as one among other diagnostic parameters. However, the detectable levels observed in all of these children support the evidence that a small amount of body fat is likely to be present in these patients, despite complete subcutaneous lipoatrophy. Our data suggest that this small amount of adipose tissue could be metabolically active and, at least in part, sensitive to insulin. Further investigations are required to uncover the pathophysiological mechanisms of this syndrome, known to be commonly associated with insulin resistance.


Introduction

Congenital generalized lipoatrophy (CGL) is a rare disorder with multiple clinical manifestations. The major features are complete atrophy of subcutaneous adipose tissue and marked insulin resistance (1–3). Atrophy was believed to be generalized to the whole body, but some authors have demonstrated the presence of fat in particular areas where adipose tissue has a mechanical function (4). In accord with the lack of subcutaneous adipose tissue, this observation led them to hypothesize that CGL may involve an abnormal development of metabolically active adipose tissue only (4). Leptin, the adipocyte-specific product of the ob gene, acts as a regulatory factor of body weight (5, 6). In children, as in adults, leptin levels are correlated with body mass index (BMI) and body fat mass (7, 8). Girls consistently demonstrate higher serum leptin levels than boys, and this gender difference persists in adulthood (7, 8). Pardini et al. (9) have demonstrated that adults with congenital or acquired generalized lipoatrophy have decreased serum leptin levels with an obvious interpretation that this is due to decreased fat mass. In order to see if leptin production is already decreased during childhood, we measured serum leptin concentrations in children with CGL and investigated the relationship between metabolic parameters and the variations in leptin levels.

Subjects and methods

Subjects

Six children (three male, three female) aged 5.5 to 11 years were studied (Table 1). All had CGL diagnosed between 2 months and 4 years of age. Five of them were born in consanguineous pedigrees. At the time of the study, all showed muscular hypertrophy, acanthosis nigricans and hepatomegaly. Four had acromegaloïd features. Five of them showed increased triglyceride
concentrations before the start of a hypotriglyceridemic diet. One female (Case 6, Table 1) was already insulin dependent. She was on a diabetic diet and receiving 6 U/kg insulin and 500 mg metformine daily. Five of them showed a normal glucose tolerance under an oral glucose tolerance test.

**Biochemical analyses**

Serum leptin concentrations were measured using a specific RIA (Lincor Research, St Charles, MO, USA) as previously described by Maffei et al. (10). Sensitivity of the assay was 0.4 ng/ml. Intra- and inter-assay coefficients of variation (CVs) were 5.2 and 8.7% respectively, at 2.3 ng/ml. An albumin solution at 50 g/l did not cross-react with the leptin antibody in this assay. In our hands, the range of leptin values during childhood is 4–8 ng/ml. Insulin concentrations were measured using a double antibody RIA (Sanofi-Pasteur, Marne la coquette, France). Sensitivity of the assay was 0.2 μU/ml. Intra- and inter-assay CVs were 3.2 and 4.8% respectively, at 71 μU/ml. Normal fasting insulin values during childhood are <15 μU/ml.

**Results**

All children had detectable serum leptin concentrations (mean 1.19 ± 0.32 ng/ml (± S.D.)) ranging between 0.76 and 1.71 ng/ml (Table 1). In order to exclude a putative non-specific cross-reaction, we measured leptin levels after a 2-fold dilution of sera. Leptin values obtained with or without dilution were strictly correlated \( r = 0.96, P < 0.001 \), which indicates a good parallelism with the standard curve.

No gender difference was observed in leptin concentrations. BMI did not significantly correlate with serum leptin levels \( r = 0.6, P = 0.2 \). In contrast, fasting serum leptin values were significantly correlated with fasting endogenous and/or exogenous insulin concentrations (log transformed) \( r = 0.83, P = 0.024 \) (Fig. 1) and tended to be correlated with fasting glucose \( r = 0.80, P = 0.055 \). No significant correlation was observed between fasting leptin values and fasting triglyceride concentrations \( r = 0.32, P = 0.25 \).

**Discussion**

One of the major findings of this study is that leptin concentrations in children with CGL (1.19 ± 0.32 ng/ml) were dramatically lower than those observed in normal children. Large inter-individual variations of leptin values are observed in children, as in adults. However, the range of mean values observed in healthy lean children was 4–8 ng/ml (7, 8, 11). Our observations are consistent with the decreased serum leptin concentrations observed by Pardini et al. in adults with CGL (9). BMI is known to be one of the major determinants of leptin values. In the present study, no correlation was found between these two parameters. This lack of association is easily explained by the presence of CGL, in which BMI mainly reflects lean body mass.

Nevertheless, leptin concentrations remained detectable. The strict correlation observed between leptin values obtained before and after a 2-fold dilution demonstrates that what we measured in serum is identical to the standard used in the RIA. We conclude therefore that leptin is really detectable in children with CGL, despite the extremely low values detected. This observation suggests that, as in adults, a small amount of adipose tissue seems to be present in these children. Garg et al. (4) have hypothesized that CGL may result in an abnormal development of metabolically active adipose tissue, whereas mechanical adipose tissue (organs, buccal region, tongue, palms, soles, scalp, perineum, periarticular regions and epidural areas) is preserved.

In healthy lean men, prolonged hyperinsulinemia is known to increase serum leptin concentrations (11–13). The correlation observed in the present study between insulin and leptin concentrations is consistent with the results of Pardini et al. (9), and suggests that in these subjects, not only is a small amount of adipose tissue present, but also that it remains sensitive enough to insulin to induce leptin secretion. Further investigations are required to document the action of insulin on this small amount of body fat. It cannot be ruled out that the ‘mechanical’ adipose tissue detected could have at least some metabolic functions. Alternatively,

<table>
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<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6*</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.5</td>
<td>6.5</td>
<td>7.0</td>
<td>5.5</td>
<td>11.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Gender</td>
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<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>18.3</td>
<td>14.4</td>
<td>18.6</td>
<td>18.0</td>
<td>18.9</td>
<td>20.3</td>
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<tr>
<td>Fasting triglycerides (mmol/l)</td>
<td>3.57</td>
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<td>0.79</td>
<td>0.90</td>
<td>1.98</td>
<td>7.51</td>
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<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>3.0</td>
<td>4.1</td>
<td>4.3</td>
<td>3.5</td>
<td>3.7</td>
<td>14.1</td>
</tr>
<tr>
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<td>32</td>
<td>42</td>
<td>50</td>
<td>150</td>
<td>153</td>
</tr>
<tr>
<td>Fasting leptin (ng/ml)</td>
<td>0.76</td>
<td>0.95</td>
<td>1.20</td>
<td>1.24</td>
<td>1.31</td>
<td>1.71</td>
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</tbody>
</table>

* Girl with diabetes.
putative undetected clusters of adipose tissue could be present and metabolically active.

In summary, extremely low leptin values measured in children with CGL could be regarded as one among other diagnostic parameters. However, detectable levels support the evidence that a small amount of body fat is likely to be present in these patients, despite the complete subcutaneous lipoatrophy. The unexpected ability of this adipose tissue to be metabolically active and, at least in part, sensitive to insulin, requires further investigation in order to uncover the pathophysiological mechanisms of this syndrome, usually known to be associated with insulin resistance.

References

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![Figure 1](https://example.com) Fasting leptin concentrations plotted against fasting insulin concentrations (log transformed) in the six children with CGL.