The Role of Leptin in Diencephalic Syndrome

abstract

Diencephalic syndrome is a rare condition associated with central nervous system tumors. The most common presentation is secondary failure to thrive with proper caloric intake and no statural impairment. Despite the importance of this syndrome, little is known of its pathophysiology. Some reports have documented changes in human growth hormone and insulin levels at the onset, whereas others have described endocrine disorders of hypothalamic insufficiency resulting from surgery of the tumor. It has been suggested that the hormonal changes described, such as increased human growth hormone and ghrelin or decreased insulin and leptin levels, are related to a patient's BMI. These findings support the role of these 4 hormones as indicators of the patient's nutritional status but not as mediators or potential therapeutic targets of the disease. We report the case of an infant who initially presented with tumor progression and, after chemotherapy, progressive weight gain and reduced tumor size. Because he presented no hormonal deficiencies or obesity after therapy, we were able to analyze his hormonal status uninfluenced by effects of metabolic treatment or excess weight. Although ghrelin and leptin levels have been related to nutritional status, our patient's leptin levels fell when tumor size decreased and weight increased: an extraordinary finding because leptin concentration is expected to increase with weight gain. This paradoxical response suggests that leptin may be dysregulated in diencephalic syndrome or that the diencephalic astrocytoma may have had an effect on leptin secretion. Pediatrics 2014;133:e263–e266
Diencephalic syndrome, first described by Russell in 1951, is characterized by severe emaciation despite normal appetite and preserved height/length curve, usually accompanied by other symptoms such as lethargy, vomiting, and nystagmus. Low-grade astrocytomas located in the diencephalic region are often associated with this syndrome.

Despite the importance of diencephalic syndrome, little is known of its pathophysiology. Some reports have documented alterations in human growth hormone (hGH) and insulin levels at the onset, whereas others have described endocrine disorders of hypothalamic insufficiency resulting from surgery of the tumor.

The latest patient admitted to our hospital with this syndrome was diagnosed with a low-grade astrocytoma, which was not resected due to its location. After an initial period of tumor growth, the patient responded well to second-line chemotherapy, with a reduction in tumor size, clinical improvement, and gradual weight recovery. Hormone monitoring of the patient provided us with an opportunity to better understand the role of metabolic hormones in a way that has not been described previously.

**PATIENT PRESENTATION**

An 8-month-old boy who had normal gestational development was admitted to the emergency department with failure to thrive (weight at diagnosis: 6.7 kg, equivalent to a $-1.9$ SD score [SDS]). On admission, he presented horizontal and rotary nystagmus of 2 months duration. His length at diagnosis was within the normal range for age (71.2 cm, $+0.5$ SDS), and he had no vomiting or other symptoms. MRI revealed a hypothalamic mass, which was later biopsy-confirmed as a grade II pilomyxoid astrocytoma (2007 World Health Organization classification).

Laboratory tests at diagnosis showed low insulin levels (<2 mIU/L), normal thyroid hormone levels (thyrotropin, T3, T4, and free T4), high hGH (20.8 ng/mL), and low insulin-like growth factor I at less than $-1$ SDS (48.9 ng/mL). In the early stage of the syndrome, leptin levels were found to be low (1.1 ng/mL) and ghrelin levels were high (1786 pg/mL) (Table 1).

Indirect calorimetry showed a slight increase in caloric wasting (117%), although it could not be measured in continuous vigil. Dual-energy radiograph absorptiometry estimated a body fat percentage of 4%, which is much lower than normal.

Given the location of the tumor, surgery was not attempted, and chemotherapy after the International Society of Pediatric Oncology (SIOP) low-grade gliomas (LGG) 2002 protocol was started. After 4 cycles of treatment, the response was poor, and the patient continued to lose weight, which decreased to 5.7 kg ($-3.3$ SDS); hence, chemotherapy was changed to the United Kingdom Children Study Group (UKCCSG)/International Society of Pediatric Oncology (SIOP) protocol. In the following months, tumor growth stopped, and weight loss reversed with a high-calorie diet (120–150 kcal/kg per day) administered by continuous enteral night feeding through a percutaneous gastrostomy.

**DISCUSSION**

Diencephalic syndrome should be ruled out in a child with emaciation, preserved height/length gain, and normal appetite. Characteristic symptoms of this syndrome include vomiting, nystagmus, seizures, paralysis, polyuria, polydipsia, and behavioral changes, which may not always be present at the diagnosis.

The catabolic state with increased basal energy expenditure of up to 50% requires a progressive caloric intake.

### Table 1 Hormone Changes, Weight Gain, and Caloric Intake at 4 Time Points

<table>
<thead>
<tr>
<th>Variable</th>
<th>8 Months</th>
<th>24 Months</th>
<th>29 Months</th>
<th>34 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>6.7</td>
<td>10</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>BMI (18.5–25)</td>
<td>13.2</td>
<td>14.8</td>
<td>15.8</td>
<td>16.5</td>
</tr>
<tr>
<td>Caloric intake (90–100 kcal/kg per day), kcal/kg per day</td>
<td>185</td>
<td>120</td>
<td>120</td>
<td>75</td>
</tr>
<tr>
<td>Body fat percentage by DXA (10%–30%)</td>
<td>4.3</td>
<td>—</td>
<td>—</td>
<td>26.8</td>
</tr>
<tr>
<td>T3 (60–181 ng/dL), ng/dL</td>
<td>222</td>
<td>324</td>
<td>207</td>
<td>196</td>
</tr>
<tr>
<td>T4 (4.5–10.9 µg/dL), µg/dL</td>
<td>13</td>
<td>13.4</td>
<td>10.8</td>
<td>9.9</td>
</tr>
<tr>
<td>TSH (0.6–6.2 µIU/mL), µIU/mL</td>
<td>1.86</td>
<td>3.4</td>
<td>0.66</td>
<td>2.25</td>
</tr>
<tr>
<td>IGF1 (127–350 ng/mL), ng/mL</td>
<td>48.8</td>
<td>—</td>
<td>—</td>
<td>182</td>
</tr>
<tr>
<td>ghrelin (&lt;6 ng/mL), ng/mL</td>
<td>20.8</td>
<td>—</td>
<td>10.2</td>
<td>0.66</td>
</tr>
<tr>
<td>Leptin (2.5–5.9 ng/mL), ng/mL</td>
<td>1.1</td>
<td>2.5</td>
<td>1.32</td>
<td>0.47</td>
</tr>
<tr>
<td>Ghrelin (1009–1461 pg/mL), pg/mL</td>
<td>—</td>
<td>1786</td>
<td>—</td>
<td>1685</td>
</tr>
</tbody>
</table>

DXA, dual-energy radiograph absorptiometry; IGF1, insulin-like growth factor I; TSH, thyrotropin; T3, triiodothyronine; T4, thyroxine; —, unmeasured levels.

* Normal reference values are shown in parentheses.
of up to 210 kcal/kg per day, which often requires percutaneous gastrostomy placement. Nevertheless, patients do not regain weight until the underlying disease has been controlled, usually by complete resection of the tumor, which is not always possible given its location. The most frequently observed tumor is grade I or grade II astrocytoma. Surgery is the first-choice treatment of these tumors. However, if the tumor cannot be completely resected, chemotherapy and radiotherapy are additional therapeutic options. The location of these tumors deep in the midline limits surgery, and early patient age at presentation limits radiation therapy.

Little is known about the mechanisms by which this tumor causes the characteristic emaciation. Drop et al hypothesized that a lipolytic peptide, B-lipotropin, which is produced in excess by the tumor or secondary to invasion, could explain the decrease in subcutaneous tissue and excess hGH release. Fleischman et al suggested a possible role of the hormones leptin and ghrelin.

In recent years, the metabolism-regulating hormones leptin (adipocyte hormone) and ghrelin (gastric hormone) have been widely studied in obesity and anorexia nervosa. Leptin stimulates thermogenesis and reduces appetite, and its plasma levels are related to BMI. In contrast, ghrelin levels fall with increasing BMI and directly stimulate hGH secretion; these 2 hormones have been related to Russell syndrome and to anorexia nervosa. Brauner et al described the changes in leptin and ghrelin levels in 11 patients with Russell syndrome before and after surgery. In all cases, leptin was low and ghrelin was high at diagnosis. After treatment, all patients had hGH and thyroid deficiencies, and 3 also had corticotropin deficiency and diabetes insipidus. In addition, all patients had a BMI >2 SDs, low ghrelin levels, and high leptin levels. The authors concluded that leptin and ghrelin are nutritional status–dependent hormones.

Our patient initially presented with tumor progression, but after second-line chemotherapy, he responded satisfactorily with a gradual weight gain and reduction in tumor size. He did not present hormonal deficiencies or obesity after treatment, which enabled us to analyze his hormone profile during tumor progression and the later improvement without the influence of other hormonal deficits or abnormally high BMI.

At diagnosis, our patient had the hormonal abnormalities described by Brauner et al (high hGH and ghrelin, low insulin and leptin), likely related to his low BMI, as described previously. Cortisol, thyroid hormones, and sex hormones were within normal limits, as described elsewhere. These data support a role for these hormones as indicators of nutritional status but not as mediators or potential therapeutic targets of the disease.

Unexpectedly, our patient’s leptin levels increased as tumor size increased, as measured by MRI. Leptin levels reached maximum concentrations at the time when tumor size was largest and the patient presented his lowest weight. The lowest leptin concentration was seen at the last follow-up examination, when tumor size was smallest and the

**FIGURE 1**
Patient outcome. A, Changes in weight, tumor size, and leptin and ghrelin levels at 4 time points of the patient’s evolution. B, T1-weighted, contrast-enhanced MRIs reveal a hyperintense hypothalamic lesion with internal areas of necrosis.
patient's weight was highest, contrary to what would have been expected if leptin concentration depended only on nutritional status. This observation leads to the question of whether diencephalic astrocytoma may directly or indirectly stimulate leptin secretion.

The fluctuations in leptin levels in our patient appear to have been influenced mainly by tumor activity. We found no evidence in the literature indicating that the chemotherapy drugs used might affect leptin concentration, and the patient had no infectious complications that could influence leptin secretion. Prospective study of leptin concentrations in future cases with similar characteristics could determine whether diencephalic astrocytoma has an effect on secretion of this hormone.

REFERENCES

# The Role of Leptin in Diencephalic Syndrome

Pablo Velasco, María Clemente, Raquel Lorite, M. Clara Ventura, Luis Gros, José Sanchez de Toledo and Soledad Gallego

*Pediatrics* 2014;133;e263

DOI: 10.1542/peds.2012-3196 originally published online December 23, 2013;

| Updated Information & Services | including high resolution figures, can be found at: [http://pediatrics.aappublications.org/content/133/1/e263](http://pediatrics.aappublications.org/content/133/1/e263) |
| **References** | This article cites 24 articles, 6 of which you can access for free at: [http://pediatrics.aappublications.org/content/133/1/e263.full#ref-list-1](http://pediatrics.aappublications.org/content/133/1/e263.full#ref-list-1) |
| **Subspecialty Collections** | This article, along with others on similar topics, appears in the following collection(s): Neurology [http://classic.pediatrics.aappublications.org/cgi/collection/neurology_sub](http://classic.pediatrics.aappublications.org/cgi/collection/neurology_sub)  
Neurologic Disorders [http://classic.pediatrics.aappublications.org/cgi/collection/neurologic_disorders_sub](http://classic.pediatrics.aappublications.org/cgi/collection/neurologic_disorders_sub)  
Pharmacology [http://classic.pediatrics.aappublications.org/cgi/collection/pharmacology_sub](http://classic.pediatrics.aappublications.org/cgi/collection/pharmacology_sub)  
Toxicology [http://classic.pediatrics.aappublications.org/cgi/collection/toxicology_sub](http://classic.pediatrics.aappublications.org/cgi/collection/toxicology_sub) |
| **Permissions & Licensing** | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: [https://shop.aap.org/licensing-permissions/](https://shop.aap.org/licensing-permissions/) |
| **Reprints** | Information about ordering reprints can be found online: [http://classic.pediatrics.aappublications.org/content/reprints](http://classic.pediatrics.aappublications.org/content/reprints) |

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2014 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
The Role of Leptin in Diencephalic Syndrome
Pablo Velasco, María Clemente, Raquel Lorite, M. Clara Ventura, Luis Gros, José Sanchez de Toledo and Soledad Gallego

Pediatrics 2014;133:e263
DOI: 10.1542/peds.2012-3196 originally published online December 23, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/133/1/e263