

## Pathogenesis of Hypothalamic Obesity in Children

The pathogenesis of hypothalamic obesity is not clear. In this multicenter study, the investigators studied the role of leptin, soluble leptin receptor (sOb-R), resistin, and insulin secretory dynamics in the development of hypothalamic obesity. Children who had hypothalamopituitary tumors were divided into 2 groups. The first group included obese-overweight (hypothalamic obese [HOB] group, n=23) and second group included non-obese children (hypothalamic non-obese [HNOB] group, n=16). Exogenously obese-overweight children (OB group, n=22) were included as controls. Oral glucose tolerance test (OGTT), basal serum leptin, sOb-R, resistin levels, and homeostasis model assessment (HOMA) indexes were compared between the groups. Age, sex, and pubertal status were similar in study groups. Median and interquartile ranges of BMI z-scores were similar in HOB and OB groups.

The ratio of the patients who received chemotherapy and radiotherapy were similar in the 2 groups. Tumor size, relapse rates, and number of operations were not different between the groups. The number of patients with multiple pituitary hormone deficiency as well as ACTH, TSH, GH, ADH, and gonadotropic hormone deficiencies were also similar in HOB and HNOB groups. Growth hormone (GH) replacement dose was 0.025–0.035 mg/kg/day for the patients with GH deficiency, and hydrocortisone replacement dose was  $\leq 10$  mg/m<sup>2</sup>/day in all patients with central adrenal insufficiency. All patients with central hypothyroidism were receiving adequate replacement dose of L-thyroxine to maintain free T<sub>4</sub> levels in the normal range.

	HOB Group	HNOB Group	OB Group
<b>Leptin/BMI</b>	4.0 (1.6–5.2)	1.5 (0.8–3.1)	2.5 (1.8–3.5)
<b>Leptin/sOb-R (FLI)</b>	2.0 (0.8–3.5)	0.6 (0.3–1.2)	1.5 (1.0–2.3)

Serum leptin levels corrected for BMI were highest and total leptin/sOb-R ratios (free leptin index [FLI]) tended to be higher in HOB than HNOB and OB groups, indicating leptin resistance (Table). Serum resistin levels were similar in all groups. Basal serum glucose, basal and second-hour insulin levels in OGTT, and HOMA index were higher in OB group than the HOB and HNOB groups, indicating insulin resistance in simple obesity; however, the increment of insulin to the same glycemic load in OGTT was highest in the HOB group indicating insulin dysregulation ( $p < 0.05$ ). It was concluded that hypothalamic obesity seemed to be related to both dysregulated afferent (leptin) and efferent (insulin) neural outputs through the autonomic nervous system resulting in energy storage as fat.

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**Editor's Comment:** Hypothalamic obesity is a frustrating syndrome which develops following an insult to the hypothalamic area.<sup>1,2</sup> The pathophysiology of this condition is not clear and therefore therapeutic attempts usually fail. There may be many confounding factors which may affect body weight and energy homeostasis all of which have been more or less controlled in this study.

In both HOB and HNOB groups, only the leptin levels were remarkably higher in the tumors with hypothalamic/thalamic involvement ( $p$  values 0.023 and 0.01, respectively). The findings of higher leptin/BMI and higher FLI in hypothalamic patients suggest the contribution of leptin resistance in the pathogenesis of hypothalamic obesity. A recent study by Shaikh et al also confirmed that hyperleptinemia is associated with obesity following hypothalamic damage in children.<sup>3</sup>

The primary defect in patients with hypothalamic obesity is believed to be altered neural regulation of the beta-cell secretion resulting in insulin hypersecretion, in contrast with simple obesity, where peripheral insulin resistance is assumed to be the primary defect driving a compensator beta-cell response. In agreement with this hypothesis, this study shows that HOMA index representing insulin resistance is higher in the common obese groups compared to the patients with brain tumors in the hypothalamo-pituitary region. This finding implies the importance of dysregulated insulin secretion to a glycemic load rather than insulin resistance in the development of hypothalamic obesity differently from exogenous obesity.

In conclusion, compared to simple obese children, HOB patients have lower HOMA and lower basal insulin, but a higher insulin response to a glycemic load and higher leptin/BMI. These findings support that in hypothalamic obesity there are both dysregulated afferent (leptin) and efferent (insulin) neural outputs through the autonomic nervous system resulting in energy storage as fat. Dysregulated insulin secretion, rather than insulin resistance, is characteristic of hypothalamic obesity. Obviously, more studies are needed to further elucidate the mechanisms of hypothalamic obesity in order to offer more rewarding therapies for the patients.

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### References

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