Recurrent, Symptomatic Fasting Hypoglycemia in Patient with Partial Hypopituitarism: Role of Increased Insulin Sensitivity: Case Report

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**ABSTRACT** Partial hypopituitarism is rarely a cause of hypoglycemia because actions of other hormones compensate for their deficiencies. A 50-year-old man was admitted to our hospital with recurrent symptomatic hypoglycemia in the fasting state for 9 years. On admission, fasting plasma glucose level was 38 mg/dL while insulin and C-peptide levels were within normal ranges. Biochemical data were normal except for dyslipidemia. Four-hour oral glucose tolerance test (OGTT) was normal but insulin sensitivity index (ISI) was increased. Hypothalamo-pituitary-adrenal (HPA) axis function was assessed with the insulin-induced hypoglycemia test (IHT). IHT demonstrated growth hormone deficiency (GHD) and secondary hypoadrenalism. Abdominal, thorax and pituitary magnetic resonance imaging (MRI) were normal. After the replacement therapy of growth hormone (GH) and cortisol, hypoglycemic episodes have never been recorded for over 13 months up to date. ISI was reduced and fasting glucose varied between 50-55 mg/dL after 3 months of treatment. We present a case of recurrent symptomatic hypoglycemia in the fasting state with an idioopathic partial hypopituitarism.

**Key Words**: Hypoglycemia; hypopituitarism


**Anahtar Kelimeler**: Hipoglisemi; hipopituitarizm


Hypoglycemia can occur under various circumstances. Deficiencies in the release of GH and cortisol is rarely a cause of hypoglycemia because actions of other hormones compensate for their deficiencies. More than 90% of patients with hypopituitarism have acquired pituitary disease, which is usually caused by a pituitary tumor, surgery, or cranial irradiation for other pathologies. We present a case of recurrent hypoglycemia that is rarely seen as a cause of hypoglycemia...
symptomatic hypoglycemia in the fasting state with an idiopathic partial hypopituitarism.

**CASE REPORT**

A 50-year-old man was admitted to our hospital with recurrent symptomatic hypoglycemia in the fasting state for 9 years. Hypoglycemia occurred particularly in the morning with blurred vision, palpitations and weakness, which resolved after oral sugar intake. He had no history of any endocrine disorders, trauma, surgery and drug use known or suspected to cause hypoglycemia. On admission, his skin was thin and dry and his blood pressure was 100/70 mmHg. He was moderately overweight (BMI: 28 kg/m²) with abdominal obesity (Waist to hip ratio: 0.91). Reduced lean body mass (52%) and increased fat mass (35%) was observed by Dual Energy X-Ray Absorption. The overnight fasting venous plasma glucose level was 38 mg/dL while insulin (5 μU/mL) and C-peptide (1.4 ng/mL) levels were within normal range. Biochemical data were normal except for dyslipidemia (triglyceride 200 mg/dL, HDL-cholesterol 30 mg/dL, LDL-cholesterol 92 mg/dL) (Table 1). Four-hour OGTT was normal. Plasma cortisol (12 μg/dL) and ACTH (5 pg/mL) levels in the morning suggested secondary hypoadrenalinism. The HPA axis response to hypoglycemia was assessed with the IHT. The diagnosis GHD and secondary hypoadrenalinism was established on the basis of an inadequate peak of GH level (0.07 μg/dL) and plasma cortisol level (14 μg/dL) while the blood glucose level achieved was below 40 mg/dL during IHT. Insulin-like growth factor-I (IGF-I: 59 ng/mL) and insulin-like growth factor-binding protein-3 (IGFBP-3: 1400 ng/mL) concentrations were low according to age adjusted values. We observed an inadequate peak of GH (0.07 ng/mL) to arginin test. Other serum pituitary hormones, counter-regulatory hormones, and plasma and urinary catecholamines were within normal ranges. Neoplastic and autoimmune markers were negative. Abdominal, thorax and pituitary MRI were normal. Insulin resistance (IR) in the fasting state was estimated by the homeostasis model assessment (HOMA) according to the formula described by Matthews et al. Global ISI was estimated by using ISI-composite derived from the OGTT proposed by Matsuda and De Fronzo. Increased insulin sensitivity (HOMA-IR 1.6, ISI 7.8) was calculated in the pretreatment period according to the values of the control group of the study, which were previously reported (Table 2).

Therefore, an inadequate peak of serum GH and cortisol during hypoglycemia indicated that he had an idiopathic partial hypopituitarism, which is a rare cause of hypoglycemia. According to these results frequent oral feeding, recombinant human GH (0.006 mg/kg/day subcutaneous) and glucocorticoid (2.5 mg prednisolone in the morning) were recommended. The dosage of GH was initiated based on the consensus of the Growth Hormo-

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**TABLE 1: Biochemical values of the patient on admission.**

<table>
<thead>
<tr>
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<th>On admission</th>
<th>Reference values</th>
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<tbody>
<tr>
<td>GH (ng/mL)</td>
<td>0.05</td>
<td>5-25</td>
</tr>
<tr>
<td>IGF-I (ng/mL)</td>
<td>59</td>
<td>70-197</td>
</tr>
<tr>
<td>IGFBP-3 (ng/mL)</td>
<td>1400</td>
<td>1700-4400</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>12</td>
<td>5-25</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>5</td>
<td>0-100</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>5</td>
<td>6-27</td>
</tr>
<tr>
<td>TSH (mU/mL)</td>
<td>2.4</td>
<td>0.27-4.2</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>1.4</td>
<td>0.65-2.3</td>
</tr>
<tr>
<td>Free T3 (ng/dL)</td>
<td>3.1</td>
<td>1.8-4.2</td>
</tr>
<tr>
<td>Fasting venous glucose (mg/dL)</td>
<td>38</td>
<td>70-110</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>1.4</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Anti-insulin ab</td>
<td>Negative</td>
<td>-Negative</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>200</td>
<td>100-1500</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>91</td>
<td>100-130</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>34</td>
<td>40-50</td>
</tr>
</tbody>
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**TABLE 2: Insulin sensitivity in the pretreatment and posttreatment period.**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Posttreatment (6 months)</th>
<th>Control (n: 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting venous glucose (mg/dL)</td>
<td>35</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.6</td>
<td>3.1</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>ISI</td>
<td>7.8</td>
<td>4.6</td>
<td>6.4 ± 0.9</td>
</tr>
</tbody>
</table>
ne Research Society. Hypoglycemic episodes have never been recorded for over 13 months up to date, after the replacement therapy. However, fasting glucose varied between 50-55 mg/dL. Higher insulin levels were observed in OGTT after the replacement therapy.

Serum IGF-I was measured by immunoradiometric assay. GH was measured by an immunometric assay (IMMULITE- DPC®, UK). Plasma glucose was immediately measured by the glucose oxidase method. Insulin was measured by fluoro-immunometric assay.

**DISCUSSION**

We considered that the cause of the hypoglycemia might be an idiopathic partial hypopituitarism due to the inadequate peak levels of GH and cortisol to hypoglycemia during IHT. In addition to, a satisfactory response to the treatment with cortisol and GH replacement was observed. His symptoms were improved. There are many causes leading to acquired hypopituitarism (eg, tumors, mechanical or compressive lesions, infarction, radiation, autoimmune, infiltrations, and infections). However he had no history of any trauma and operation.

GH and cortisol have been demonstrated to contribute independently to glucose counterregulation via their actions to promote glucose release and limit glucose uptake. Deficiencies of these hormones can diminish the amounts and activities of the enzyme involved in gluconeogenesis and the hepatic capacity for glucose output. Although theoretically, deficiencies in any of the hormones may cause hypoglycemia, this is unusual in the absence of diabetes mellitus. However, combined deficiencies of these hormones may rarely cause spontaneous hypoglycemia. A case of acquired isolated adultonset GHD with symptomatic hypoglycemia was recently reported.

Hypoglycemia in this patient often developed after a period of fasting, during an exercise or illness. These conditions stimulate glucose utilization and diminish glycogen stores. Symptomatic hypoglycemia did not occur in this patient after GH and cortisol replacement therapy. Hypoglycemia was usually corrected with glucocorticoid replacement whereas GH replacement had a lesser effect.

Under normal condition, keton bodies are produced for oxidation during fasting, sparing glucose to be used as fuel by the brain. GH has a direct ketogenic effect on the liver releasing ketones during fasting. GHD may increase glucose consumption. This patient also had relative hypoketonemia during hypoglycemia.

Fasting hypoglycemia may occur in infants and children with chronic deficiencies of these hormones particularly after a period of fasting and during an illness. The likely explanation of hypoglycemia is a defect in gluconeogenesis and increased insulin sensitivity. GH and cortisol have insulin antagonistic effects; hence insulin sensitivity is decreased in acromegaly, puberty and GH and cortisol replacement therapy. Therefore increased insulin sensitivity may be expected in this patient.

It is known that counterregulatory hormones such as cortisol, GH and epinephrine act to temper tissue sensitive to insulin. GH and cortisol suppress insulin mediated glucose uptake and augment glucose release, which may explain hypoglycemia in children with GHD. Moreover recently published studies indicated that children with GHD had decreased fasting glucose levels, decreased insulin secretion, and increased insulin sensitivity with increased glucose utilization and blunted hepatic glucose release.

On the contrary, adults with GHD were shown to be insulin resistant. The etiology of IR in hypopituitary patients is related to abnormal body composition and the deficiency of GH and replacement of other hormones.

After the GH and cortisol replacement therapy, insulin sensitivity decreased and hypoglycemic episodes have not been recorded for over 13 months up to date in this patient (Table 2). We titrated the dosage of GH according to IGF-1 and clinical symptoms so we did not observe the features of metabolic syndrome. Our results were similar to
those in the case published by Pia et al.\textsuperscript{14} Furthermore increased insulin sensitivity was reported in adult onset GHD in patients with GHRH receptor defect and type 1 diabetes.\textsuperscript{11}

In conclusion, idiopathic partial hypopituitarism is a rare cause of hypoglycemia. Prolonged fasting and predisposition to hypoglycemic factors including exercise, infection and stress may lead to hypoglycemia in this patient. These conditions diminish glycogen storage by increasing glucose utilization. Increased insulin sensitivity may contribute to the hypoglycemic episodes. We suggest that after the elimination of other causes of hypoglycemia, provocative tests for diagnosis of hypopituitarism should be run when suspected since response to therapy is satisfactory.

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REFERENCES
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