OLGU SUNUMU CASE REPORT

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

Tekrarlayan Semptomatik Açlık Hipoglisemisi Olan Parsiyel Hipopituitarizmli Hasta: Artmış İnsülin Sensitivitesinin Rolü

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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-peptid 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 idiopathic partial hypopituitarism.

Key Words: Hypoglycemia; hypopituitarism

ÖZET Parsiyel hipopituitarizm hipogliseminin nadir nedenlerinden birisidir çünkü diğer hormonlar eksik olanları kompanse eder. Elli yaşında erkek hasta 9 yıldır devam eden açlıkta tekrarlayan semptomatik hipoglisemi atakları ile hastaneye başvurdu. Başvuruda, açlık plazma glukozu 38 mg/dL bulundu. İnsülin ve C-peptid düzeyleri normal sınırlardaydı. Biyokimyasal veriler dislipidemi dışında normaldi. Dört saatlik oral glukoz tolerans testi (OGTT) normal sınırlardaydı fakat insülin sensitivitesi (ISI) artmıştı. Hipotalamo-pituiter-adrenal (HPA) aks fonksiyonu insülin hipoglisemi test (IHT) ile değerlendirildi. IHT sonuçlarına göre growth hormon eksikliği (GHD) ve sekonder hipoadrenalizm olduğu düşünüldü. Abdominal, toraks ve pituiter magnetik rezonans görüntüleme (MRI) normaldi. GH ve kortizol replasman tedavisi başlandı. Tedaviyi takiben 13 aydır hipoglisemik ataklar tekrarlamadı. Tedavinin 3. ayında ISI azaldı ve açlık glukoz düzeyi 50-55 mg/dL arasında seyretti. Açlıkta tekrarlayan semptomatik hipoglisemileri olan idiyopatik parsiyel hipopituitarizmi olan bu olgu sunuldu.

Anahtar Kelimeler: Hipoglisemi; hipopituitarizm

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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.[1-3] We present a case of recurrent

TABLE 1: Biochemical values of the patient on admission.

	On admission	Reference values
GH (ng/mL)	0.05	5-25
IGF-I (ng/mL)	59	70-197
IGFBP-3 (ng/mL)	1400	1700-4400
Cortisol (µ/dL)	12	5-25
ACTH (pg/mL)	5	0-100
Insulin (uIU/mL)	5	6-27
TSH (IU/mL)	2.4	0.27-4.2
Free T4 (ng/dL)	1.4	0.65-2.3
Free T3 (ng/dL)	3.1	1.8-4.2
Fasting venous glucose (mg/dL)	38	70-110
C-peptide (ng/mL)	1.4	0.5-2
Anti-insulin ab	Negative	-Negative
Triglyceride (mg/dL)	200	100-1500
LDL-cholesterol (mg/dL)	91	100-130
HDL-cholesterol (mg/dL)	34	40-50

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/m^2) 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 hypoadrenalism. The HPA axis response to hypoglycemia was assessed with the IHT. The diagnosis GHD and secondary hypoadrenalism 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[4] Global ISI was estimated by using ISI-composite derived from the OGTT proposed by Matsuda and De Fronzo.[5] 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).[6]

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 glucocor-ticoid (2.5 mg prednisolone in the morning) were recommended. The dosage of GH was initiated based on the consensus of the Growth Hormo-

TABLE 2: Insulin sensitivity in the pretreatment and posttreatment period.

	Baseline	Posttreatment (6 months)	Control (n: 29)
Fasting venous glucose (mg/dL)	35	60	70
HOMA-IR	1.6	3.1	2.2 ± 0.4
ISI	7.8	4.6	6.4 ± 0.9

ne Research Society.[7] 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 fluoroimmunometric 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).[8] 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.[9,10] Although theoretically, deficiencies in any of the hormones may cause hypoglycemia, this is unusual in the absence of diabetes mellitus.[11] However, combined deficiencies of these hormones may rarely cause spontaneous hypoglycemia.[12,13] A case of acquired isolated adultonset GHD with symptomatic hypoglycemia was recently reported.[14]

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.[15]

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 consumptions.[16] 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.[17] 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.[18-20] 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,1-3 which may explain hypoglycemia in children with GHD.[17] 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 relase.[21]

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.[1,6,12,17]

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[14] Furthermore increased insulin sensitivity was re-ported in adultonset GHD in patients with GHRH receptor defect and type 1 diabetes.[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 conribute to the hypoglycemic episodes. We suggest that after the elimination of other causes of hypoglycemia, provocative tests for diagnosis of hypopituitarysm should be run when suspected since response to therapy is satisfactory.

REFERENCES

1. Baumann G. Growth hormone and its disorders. In: Becker KL, ed. Principles and Practice of Endocrinology and Metabolism. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.p.129-45.
2. Service FJ. Medical Progress: Hypoglycemic Disorders. N Engl J Med 1995;332:1144-52.
3. Service FJ. Clinical review 42: Hypoglycemias. J Clin Endocrinol Metab 1993;76:269-72.
4. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
5. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22: 1462-70.
6. Spina LD, Soares DV, Brasil RR, da Silva EM, Lobo PM, Conceição FL, Vaisman M. Glucose metabolism and visceral fat in GH deficient adults: 1 year of GH replacement. Growth Horm IGF Res 2004;14:45-51.
7. Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. J Clin Endocrinol Metab 1998;83:379-81.
8. Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumours in adults. Q J Med 1989;70:145-60.
9. Landau BR, Wahren J, Chandramouli V, Schumann WC, Ekberg K, Kalhan SC. Contributions of gluconeogenesis to glucose production in the fasted state. J Clin Invest 1996;98:378-85.
10. Bolli GB, Fanelli CG. Physiology of glucose counterregulation to hypoglycemia. Endocrinol Metab Clin North Am 1999;28:467-93.
11. Christ ER, Simoson HL, Bren L, Sonksen PH, Russell Jones DL, Kohner EM. The effect of growth hormone replacement therapy in adult patients with type 1 diabetes mellitus and GH deficiency. Clin Endocrinol (Oxf) 1994;41:315-22.
12. Melmed S, Kleinberg D. Anterior pitutiary. In: Larsen PR, Kronenberg HM, eds. Williams Textbook of Medicine.10th ed. Philadelphia: Saunders; 2002.p. 226-9.
13. Cikim A, Dikilitas M, Cikim K. Hypopituitarism in older adults. The report of five cases with different presentations. Geriatrics 2006;61:32-5.
14. Pia A, Piovesan A, Tassone F, Razzore P, Visconti G, Magro G, et al. A rare case of adulthood-onset growth hormone deficiency presenting as sporadic, symptomatic hypoglycemia. J Endocrinol Invest 2004;27:1060-4.
15. Haymond MW, Karl I, Weldon VV, Pagliara AS. The role of growth hormone and cortisone on glucose and gluconeogenic substrate regulation in fasted hypopituitary children. J Clin Endocrinol Metab 1976;42:846-56.
16. Wolfsdorf JI, Sadeghi-Nejad A, Senior B. Hypoketonemia and age-related fasting hypoglycemia in growth hormone deficiency. Metabolism 1983;32:457-62.
17. Johansson JO, Fowelin J, Landin K, Lager I, Bengtsson BA. Growth hormone-deficient adults are insulin-resistant. Metabolism 1995;44:1126-9.
18. Møller N, Schmitz O, Jøorgensen JO, Astrup J, Bak JF, Christensen SE, et al. Basal- and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. J Clin Endocrinol Metab 1992;74:1012-9.
19. Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV. Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. J Clin Endocrinol Metab 1991;72:277-82.
20. Aman J, Rosberg S, Albertsson-Wikland K. Effect of growth hormone treatment on insulin secretion and glucose metabolism in prepubertal boys with short stature. Eur J Endocrinol 1994;131:246-50.
21. Husbands S, Ong KK, Gilbert J, Wass JA, Dunger DB. Increased insulin sensitivity in young, growth hormone deficient children. Clin Endocrinol (Oxf) 2001;55:87-92.