

A Case with Insulinoma Experiencing Syndrome of Inappropriate Secretion of ADH

İnsülinoma ve Eşlik Eden Uygunsuz ADH Sendromu Olan Olgu

Özgür Demir, Müyesser Saykı Arslan, Rifat Emral

Ankara University, School of Medicine, Endocrinology and Metabolic Diseases, Ankara, Turkey

Abstract

We report a case of thirty-five years old woman with insulinoma, syndrome of inappropriate secretion of antidiuretic hormone (SIADH). She had a previous history of epidural hematoma operation. She was given oxcarbazepine 300 mg/day because of epilepsy. At the third month of the treatment the patient referred to our clinic with tonic-clonic convulsion, hypoglycemia (serum glucose level of 34 mg/dl) and hyponatremia (118 mEq/l) were detected. The biochemical diagnosis of hypoglycemia was established in the third hour of prolonged fasting test when blood glucose level was 32 mg/dl, serum insulin level was 26.5 µIU/ml, C-peptid was 6.8 ng/ml, the insulin/glucose ratio was 0.82. Endoscopic ultrasonography detected 18x19 mm lesion in pancreas. Hyponatremia was diagnosed as SIADH after excluding other possible etiologies of hyponatremia. Because of hyponatremic effect of oxcarbazepine, it was changed with valproate sodium. Water restriction therapy was applied. After enucleation of insulinoma, hyperglycemia persisted for a week, but there was no need for insulin and plasma glucose levels never exceeded 250 mg/dl. Then sustained improvement in hypoglycemic attacks and hyponatremia has been observed. Thus the patient was cured and remained euglycemic. Although oxcarbazepine was started again, hyponatremia did not reoccur. Hypoglycemia stimulates the secretion of neurotransmitter and neuropeptides including arginine-vasopressin (AVP), but hypoglycemia related hyponatremia has not been reported up to now. This is the first case with insulinoma presenting with persisting hyponatremia and improving after insulinoma resection. *Türk Jem 2009; 13: 34-6*

Key words: Insulinoma, syndrome of inappropriate antidiuretic hormone secretion

Özet

İnsülinoma ve uygunsuz antidiüretik hormon (ADH) sendromunun birlikte görüldüğü 35 yaşında bir kadın olgu sunulmaktadır. Epidural hematoma ameliyatı öyküsü olan hastaya ilk olarak epilepsi tanısıyla oxcarbazepin 300 mg/gün başlanmıştır. Tedavinin dokuzuncu ayında tonik-klonik konvülsiyon ile başvuran hastada, hipoglisemi (plazma glukozu 34 mg/dl) ve hiponatremi (118 mEq/L) saptanmış ve ileri inceleme için yapılan uzamış açlık testinin 3. saatinde plazma glukozunun 32 mg/dl'e düşmesi sırasında bakılan serum insülin düzeyi 26.5 µIU/ml ve C-peptit düzeyi 6.8 ng/ml olarak tespit edilmiştir. Endoskopik ultrasonografide pankreasda 18x19 mm'lik lezyon saptanmıştır. Hiponatreminin diğer olası nedenleri dışlandıktan sonra hiponatremi uygunsuz ADH sendromuyla ilişkilendirilmiştir. Hiponatremik etkisi nedeniyle oxcarbazepin kesilerek tedavi valproat ile değiştirilmiştir. Su kısıtlama tedavisi uygulanmıştır. İnsülinomanın enükleasyonunu takiben bir hafta süreyle sebat eden bir hiperglisemi görülmüş ancak insülin ihtiyacı olmamış ve plazma glukoz düzeyleri hiçbir zaman 250 mg/dl'yi geçmemiştir. Sonrasında hipoglisemik ataklar ve hiponatremi kalıcı olarak düzelmiştir. Hasta kür olmuş ve öglisemik seyretmiştir. Oxcarbazepin, tekrar başlanmasına rağmen hiponatremi tekrarlamamıştır. Hipoglisemi, nörotransmitterlerin ve arginin-vazopresini içeren nöropeptitlerin salgısını uyarır ancak hipoglisemi ilişkili hiponatremi şimdiye kadar bildirilmemiştir. Bu olgu, insülinomanın cerrahi olarak çıkarılmasını takiben düzelen inatçı hiponatremi ile seyreden ilk insülinoma olgusudur. *Türk Jem 2009; 13: 34-6*

Anahtar kelimeler: İnsülinoma, uygunsuz antidiüretik hormon sendromu

Introduction

Spontaneous fasting hypoglycemia in an otherwise healthy adult is most commonly due to insulinoma, an insulin-secreting tumor

of the islets of Langerhans in pancreas (1,2). The most common clinical symptoms are due to the effect of hypoglycemia on the central nervous system (neuroglycemic symptoms), and include confusion, headache, disorientation, visual difficulties, irrational

behaviour, or even coma. Also, most patients have symptoms due to excess catecholamine release secondary to the hypoglycemia, including sweating, tremor, and palpitations. Characteristically these attacks are associated with fasting (3). Insulinomas secrete additional hormones such as gastrin, adrenocorticotrophic hormone, glucagon, human chorionic gonadotropin and somatostatin. The biochemical diagnosis is established during prolonged fasting (up to 72 hours) in 95% of the patients. The ratio of insulin ($\mu\text{U}/\text{ml}$) to plasma glucose (mg/dl) is diagnostic. In patients with insulinoma, the ratio rises during fasting (>0.25). Insulinoma resection is currently the therapy of choice (4).

SIADH is a relatively rare syndrome that has been associated with neurosurgery, hemorrhagic stroke, brain tumors, central nervous system infections, and respiratory infection (5). SIADH is also reported to be associated with the use of some drugs, e.g., neuroleptics such as oxcarbazepine, thiazides, etc. (6).

Hypoglycemia stimulates AVP secretion through a mechanism that does not involve osmotic or hemodynamic alterations but rather involves the creation of intracellular glycopemia (7,8).

Despite the known effect of hypoglycemia on AVP secretion, no case of SIADH or hyponatremia has been reported in an individual with insulinoma in the literature. The following is a case report of a patient with insulinoma and coexisting SIADH.

Case Report

A 35-year-old woman was hospitalized for investigation of the etiology of her hypoglycemia. She had a medical history of epidural hematoma operation and hypertension one year before the hospitalization. At the second month of the cranial operation, she began to complain of weakness, dizziness, blurred vision, mild agitation. Especially in the mornings, she experienced slurred speech and a seizure. She was diagnosed as epilepsy and was given oxcarbazepine 300 mg per day. Her symptoms gradually increased up to twice a week. At the ninth month of the therapy she was admitted to the Emergency Department of Ankara University, School of Medicine, with a tonic-clonic convulsion. The plasma glucose concentration of the patient was found to be 34 mg/dl. So she was transferred to the Department of Endocrinology and Metabolic Diseases for advanced evaluation. Physical examination revealed a body mass index of $30.5 \text{ kg}/\text{m}^2$. Her blood pressure was 120/80 mmHg; pulse was 84 beats per minute; temperature was 36.9°C ; respiratory rate was 16 per minute. She had an operation scar on the temporoparietal side of the cranium. Abdominal and neurological examinations were normal. Laboratory investigations were as follows: Haematocrit was 30.2%, haemoglobin was 9.8 g/dl, and white blood cell count was 5930 per mm^3 . Her sodium level was 123 mEq/L (normal range 136-145 mEq/L), potassium level was 4.6 mEq/L (normal range 3.5-5.1 mEq/L), blood urea nitrogen was 4 mg/dl (normal range 6-20 mg/dl). Because hyponatremia was noticeable, we tried to find out its etiology. Serum osmolarity was found to be as low as 242 mosm/kg (normal range 275-295 mosm/l). Twenty-four hour urine was collected and the urine sodium excretion was found to be 126 mEq/L (normal range 40-220 mEq/L), and the urine osmolarity was 701 mosm/kg (normal range 50-1200 mosm/kg), while urine creatinine was 990 mg/day. Her adrenocorticotrophic hormone (ACTH) level was 52.4 pg/ml (normal range 5-50 pg/ml), plasma cortisol level was 18.51 (6.2-19.4) in the early

morning. This made the diagnosis of possible adrenocortical deficiency unlikely. Thyroid function tests were all within normal ranges.

For the diagnosis of epilepsy, electroencephalography (EEG) and cranial imaging were performed. No interictal activity was recorded during normal and sleeping EEG. Bitemporalparietal bone defect secondary to operation was seen in cranial computed tomography. In order to find the reason for hyponatremia, we did some more biochemical tests. Repeated serum sodium level was 118 mEq/L. Due to hyponatremic effect of oxcarbazepine, it was stopped and changed with valproic acid. We administered hypertonic (3%) saline infusion; the control serum sodium level was 123 mEq/L. Fluid restriction was started, which improved the hyponatremia, but the sodium levels did not normalize.

For the diagnostic evaluation of hypoglycemia, a prolonged fasting test was done. During prolonged fasting test, a typical hypoglycemic attack developed in the third hour, so the test was immediately terminated. Along with concomitant blood glucose level of 32 mg/dl, serum insulin level was 26.5 $\mu\text{U}/\text{ml}$, C-peptid was 6.8 ng/ml, and the insulin/glucose ratio was 0.82, confirming the diagnosis of insulinoma. For the localization of the tumor, endoscopic ultrasound was performed and a 18x19 mm lesion in the pancreatic neck was detected. The patient underwent surgery. Tumor was found and enucleated. Pathology confirmed the diagnosis of insulinoma. After the operation, hyperglycemia developed and persisted for a week, but there was no need for insulin application; plasma glucose levels never exceeded 250 mg/dl. In the follow up period she became euglycemic. Serum sodium levels were all found to be within normal ranges postoperatively (138 mEq/L, just after the operation), although fluid restriction was stopped and she was again given oxcarbazepine for epilepsy.

Surgical removal of the tumor led to full remission of the preoperative symptoms and signs associated with hypoglycemia and hyponatremia in this patient.

Discussion

Insulinoma is the most common cause of tumor-induced hypoglycemia (1,2). The tumor may secrete insulin in short bursts, causing episodic hypoglycemia (4). Hypoglycemia causes adrenalin release, so adrenergic symptoms occur. Central nervous system dysfunction, known as neuroglycopenic symptoms, was temporally seen during prolonged fasting (4).

SIADH is the most common neuroendocrine complication following traumatic brain injury, and its prevalence is as high as 33% (9). Oxcarbazepine, an aketo-analogue of carbamazepine, was approved for the treatment of seizures of partial onset (10). Hyponatremia after the use of oxcarbazepine is usually benign and asymptomatic as long as the acute water intoxication is effectively treated (11). Pendleburg and colleagues showed that the mean plasma sodium level fell from 137.5 mEq/L to 128.5 mEq/L in patients taking oxcarbazepine (12). In the literature oxcarbazepine-induced hyponatremia is not attributed to inappropriate secretion of AVP. Possible mechanisms include a direct effect of oxcarbazepine on the renal collecting tubules or an enhancement of their responsiveness to circulating AVP (13). Conversely in the literature, a case of inappropriate secretion of AVP after exposure to oxcarbazepine was reported (14). As the

patient remained hyponatremic after the discontinuation of oxcarbazepine, and hyponatremia did not relapse after the oxcarbazepine administration following the surgical treatment of insulinoma, it can not be the cause of hyponatremia in our patient. It is important to recognize a paraneoplastic hormonal syndrome depending on the secretion of AVP by the tumor. By far, the most common tumor associated with SIADH is small cell lung carcinoma (15). In the non-tumoral causes of SIADH, like head trauma, pneumonia, and chlorpropamide therapy, the plasma and urinary AVP concentrations are generally within normal ranges (16). As our patient was normonatremic after the epidural hematoma operation, it was hard to say that epidural hematoma was the underlying cause. Surgical removal of the tumor led to full remission of hyponatremia, so the secretion of AVP by the tumor might be suspected. We can not fully exclude the possibility of ectopic AVP secretion from the tumor, because we had not made immunohistochemical analysis for AVP postoperatively. However as the serum AVP level was in normal limits (2,5 pg/mL; normal range: 0-8 pg/mL), this was unlikely, in our opinion.

Hypoglycemia stimulates AVP secretion through a mechanism that does not involve osmotic or hemodynamic alterations but rather involves the creation of intracellular glycopeptin (17,18). AVP secretion has been dissociated from peripheral mechanisms of control and is under the control of central nervous system pathways whose functions are sensitive to changes in glucose metabolism (19). Seckl et al. investigated the AVP response to insulin-induced hypoglycemia in children. 14 children without diabetes insipidus or hypothalamo-pituitary dysfunction were enrolled into the study. The results suggested that insulin-induced hypoglycemia does not reliably stimulate AVP secretion in children (20). Kamoi et al. suggested that the mild hypoglycemia observed in two patients diagnosed adrenal insufficiency might be a primary stimulus for AVP secretion (21).

In the literature, there is no reported case diagnosed as insulinoma associated with SIADH. From this point of view, this is the first case with insulinoma presenting with persisting hyponatremia and improving after the insulinoma resection. In our opinion, the reason beyond this pathological condition was the hypoglycemia induced hyponatremia. Whether hypoglycemia causes hyponatremia through a mechanism via AVP stimulation directly from the central nervous system or some other peripheral mechanisms are involved in this situation is the matter of debate.

References

1. Bower BF, Gordan GS. Hormonal effects of nonendocrine tumors. *Annual Review of Medicine*, February 1965; 16: 83-118.
2. Greenspan SF, Gardner GD. Hypoglycemic disorders. *Basic & Clinical Endocrinology*. Seventh edition. 2001, 747.
3. Jensen T.R. Endocrine tumors of gastrointestinal tract and pancreas, in *The Harrison's Principles of Internal Medicine*, 16 th ed., pp 2227.
4. Radebold K. Insulinoma. Online.
5. Newell-Price J, Beser M. *Oxford Textbook of Medicine*, 4 th edition. Eds; Warrel DA et al. OUP 2003.
6. Van Amelsvoort T, Bakshi R, Devaux CB, et al. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. *Epilepsia* 1994; 35: 181-8.
7. Baylis PH, Heath DA. Plasma arginine vasopressin response to insulin induced hypoglycemia. *Lancet* 1977; 428-30.
8. Baylis PH, Zerbe RL, Robertson GL. Plasma arginine vasopressin response to insulin induced hypoglycemia in man. *J Clin Endocrinol Metab*. 1981; 53: 935-40.
9. Klein MJ, Potter PJ. Posthead injury endocrine complications. *Emedicine*
10. Beydoun A. Safety and efficacy of oxcarbazepine : results of randomized, double-blind trials. *Pharmacotherapy* 2000; 20: 152-8.
11. Dam M. Practical aspects of oxcarbazepine treatment. *Epilepsia* 1994; 35: 23-5.
12. Pendlebury SC, Moses DK, Eadie MJ. Hyponatremia during oxcarbazepine therapy. *Hum Toxicol* 1989; 8: 337-44
13. Sachedo CR, Wasserstein A, Mesenbrink JP, Souza J. Effects of oxcarbazepine on sodium concentration and water handling. *Ann Neurol* 2002; 51: 613-20.
14. Cilli AS, Algun E. Oxcarbazepine-induced syndrome of inappropriate secretion of antidiuretic hormone. *J Clin Psychiatry*. 2002 Aug; 63: 8
15. Andree CD Bustros, Baylin SB. Endocrine manifestations of cancer. *Best practice of medicine*. 1999 Oct.
16. Manoojian C, Pandian M, Ehrlich I, Fisher D, Horton R. Plasma atrial natriuretic hormone levels in patients with the syndrome of inappropriate antidiuretic hormone secretion. *J Clin Endocrinol Metab*. 1988;67: 571-5.
17. Baylis PH, Zerbe RL, Robertson G.L. Arginine vasopressin response to insulin-induced hypoglycemia in man. *J Clin Endocrinol Metab*. 1981; 53: 935-40.
18. Baylis PH, Heath DA. Plasma arginine-vasopressin response to insulin-induced hypoglycemia. *Lancet*. 1977; 310: 428-30.
19. Thompson DA, Campbell RG, Lilliviat U, Welle, Robertson GL. Increased thirst and plasma arginine vasopressin levels during 2-deoxy-d-glucose-induced glucoprivation in humans. *J Clin Invest*. 1981; 67: 1083-93.
20. Seckl JR, Dunger DB, Huen K, Lightman L. The plasma arginine vasopressin response to insulin-induced hypoglycemia in children with short stature is related to age and the onset of puberty. *Clin Endocrinol (Oxf)*. 1987; 26: 347-53.
21. Kamoi K, Tamura T, Tanaka K, Ishibashi M, Yamaji T. Hyponatremia and osmoregulation of thirst and vasopressin secretion in patients with adrenal insufficiency. *Clin Endocrinol Metab*. 1993; 77: 1584-8.