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Reactive Hypoglycemia Associated with Mild Adrenal Dysfunction, So-called Adrenal Fatigue

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Authors' contributions

This work was carried out in clinical collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

We here described a case of a 38-year-old woman who was referred to our hospital for general malaise, slight fever, and palpitations after a meal for the past several years. She became hungry at approximately 3:00 or 4:00 p.m. every day, and simultaneously felt the urge to eat something sweet. During a five-hour 75g OGTT test, her blood glucose level dropped sharply twice (79 mg/dL at 60 min and 76 mg/dL at 300 min) due to the excessive secretion of insulin (29.9μU/mL at 30 min and 43.1μU/mL at 120 min). She was diagnosed with a mild adrenal insufficiency due to a decrease in her serum cortisol value in the early morning and an insufficient response to the rapid ACTH stress test. We speculated that the reactive hypoglycemic symptoms observed in this patient may have developed due to the inadequate secretion of serum cortisol as a counter-regulation against insulin, which resulted in a relative excess of serum insulin after a meal. Her clinical manifestations and laboratory data were similar to a state called adrenal fatigue. Since the presentation of mild adrenal insufficiency is often insidious and difficult to recognize, careful

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examinations are required to prevent a delay in diagnosing this condition. We here described an educative case of reactive hypoglycemia associated with so-called adrenal fatigue, and recommended a thorough examination.

Keywords: Reactive hypoglycemia (postprandial hypoglycemia); adrenal fatigue; adrenal insufficiency; 75g oral glucose tolerance test (OGTT); attention-deficit hyperactivity disorder (ADHD); adrenocorticotrophic hormone (ACTH) stimulation test.

1. INTRODUCTION

Adrenal insufficiency is the clinical manifestation of the deficient production or action of glucocorticoids. It is a life-threatening condition caused by either primary adrenal failure or secondary adrenal disease due to an impairment in the hypothalamic-pituitary axis [1,2]. Genetic disorders, infections, and medications need to be considered as the underlying disease of adrenal insufficiency [3]. Adrenal insufficiency is diagnosed by blood tests and adrenocorticotrophic hormone (ACTH) stimulation tests that show inadequate levels of adrenal hormones. However, patients with indefinite symptoms that are similar to those of adrenal insufficiency have not always been diagnosed with adrenal insufficiency because they have intact hypothalamic-pituitary-adrenal axis function and a normal response to corticotropin stimulation tests. Adrenal fatigue is a collective term of nonspecific symptoms, such as body aches, fatigue, nervousness, sleep disturbances, and digestive problems, but it is not accepted as an official medical term [4]. On the other hand, reactive hypoglycemia (or postprandial hypoglycemia) is a medical term that is used to describe a condition in which blood glucose levels typically drop within four hours of eating. However, there are currently no reliable diagnostic criteria for reactive hypoglycemia because the presence of postprandial sympathoadrenal symptoms does not necessarily concur with low blood glucose levels [5]. We here described a case of reactive hypoglycemia associated with so-called adrenal fatigue.

2. CASE REPORT

A 38-year-old Japanese woman presented to our hospital with low-grade fever, general malaise, and palpitation after a meal for the past several years. She did not have developmental problems in early childhood, but was diagnosed with attention-deficit hyperactivity disorder (ADHD) at the age of 14. She has since had repeated episodes of anxiety and depression. She was unlikely to have impaired bowel movements or function because she had no history of gastrointestinal surgery. She was not and had not been pregnant or given oral hormonal contraceptives. She was not lactating on admission. Her father had also been diagnosed with ADHD; however, his clinical course was unknown. Her food preference suddenly changed a year and a half ago, and she began to consume sugary foods more frequently than before. She gained 3kg over the previous three months. Fainting, possibly due to hypoglycemia, occurred three times before she presented to us. Since she had some concerns over her health, she visited a nearby clinic five months before being hospitalized. The 75g oral glucose tolerance test (OGTT) (Table 1-A) and various endocrine examinations were performed on an outpatient basis. OGTT revealed that her blood glucose level at 60min dropped sharply (52mg/dl) while her insulin level at 30 min increased (62.6μU/mL). The results of an adrenal function test in the day time (the time blood was collected was not clear) showed that serum cortisol and ACTH levels were 3.7μg/dL and 20pg/mL, respectively. Reactive hypoglycemia due to mild adrenal insufficiency was suspected based on these test results and clinical manifestations. She was referred to a university hospital for further examinations three months before being hospitalized, but she did not visit the hospital.

On admission at our hospital, she was slightly obese with a body-mass index of 27.0, and her skin was not pathologically dark. Her vital signs were as follows: body temperature, 36.2℃; heart rate, 65 beats/min; SpO2, 98% (on room air); respiratory rate, 14 breaths/min; and blood pressure, 122/84mmHg. Laboratory tests revealed the following: total white blood cell count, 5,300/mm (differential leukocyte count: neutrophils 48.7%, eosinophils 6.6%, lymphocytes 39.3%, monocytes 4.7%, basophils 0.7%), Hb 8.8 gm%, Hb 14.0g/dL, BUN 9.4mg/dL, Cr 0.83mg/dL, Na 142.9mEq/L, K 3.96mEq/L, Cl 106.4mEq/L, Ca 9.0mg/dL, albumin 3.8g/dL (3.8-5.3), glucose 72mg/dL,

and HbA1c 4.9% (4.6-6.2). Her glycoalbumin value was slightly decreased at 11.74% (12.30-16.50). The Value of antibody to insulin was within normal range. An examination of blood lipid levels and thyroid function tests revealed normal results. Arterial blood gas values and urinalysis were also within normal ranges. All the results of the blood test, except blood gas analysis, were obtained by venipuncture. Electrocardiography, chest X-ray, head CT scans, and pituitary MRI were normal. Her serum cortisol level and ACTH level at 8: 00 a.m. on admission were 6.0μg/dL (4.0-19.3) and 38.7pg/mL (7.2-63.3), respectively (Table 2-A). Serum cortisol concentrations are generally high in the early morning, and normally range between 10 and 20 μg/dL [1,6]. Therefore, this patient's serum cortisol level in the early morning was regarded as being low. The range of normal serum cortisol concentrations at 4 p.m. is 3 to 10μg/dL. The concentrations become the lowest (less than 5μg/dL) one hour after falling asleep because of changes in the manifestation of the circadian rhythm in ACTH secretion [7]. In this patient, serum cortisol levels at16:00 and 23:00 were 4.2μg/dL and 0.6μg/dL, respectively. These could not be definitely considered as abnormal values (Table 2-A). The early morning fasting values of other hypophyseal hormones, including GH, LH/FSH, TSH, and PRL, were within normal ranges. The ACTH challenge test was performed to evaluate adrenal reserves and responsiveness because the blood cortisol level in the early morning was low. Cortisol levels at the beginning, 30 minutes, and 60 minutes after the administration of 0.25mg tetracosactide acetate (Daiichi Sankyo) were 6.2μg/dL, 13.2μg/dL, and 16.6μg/dL respectively. Rapid ACTH stimulation tests showed an inappropriate increase in cortisol levels, while her ACTH level was within the normal range at baseline (Table 2-B). Further examinations are generally needed to establish a diagnosis when the symptoms of adrenal insufficiency are present and the 8 a.m. serum cortisol value is less than 10μg/dL or the 24-hour urinary free cortisol value is less than 50μg/24 hours [8]. In addition, the possibility of primary adrenal insufficiency is considered to be improbable if the maximum value of cortisol after the rapid ACTH stimulation test is equal to or higher than 18μg/dL and the increase from baseline 60 minutes after the administration is equal to or higher than 5μg/dL. In this case, the peak value (16.6μg/dL) 60 minutes after the administration was lower than 18μg/dL. The average value of the two examinations of urinary free cortisol in the 24-hour urine collection was 16.3μg/day, which was within the lower limit of normal (11.2-80.3μg/day). We could not make a definite diagnosis of primary adrenal insufficiency based on these results.

Postprandial or reactive hypoglycemia was suspected from symptoms such as changes in food preferences and severe fatigue 3-4 hours after lunch, and episodes of being transported to the emergency department because of unconsciousness due to hypoglycemia. Since our patient was more likely to be hypoglycemic within 5 hours of eating a meal, we performed an extended five-hour 75g OGTT in order to reproduce her symptoms (Table 1-B). The plasma glucose concentration of 81 mg/dL at the basic level of preload increased to 124 mg/dL at 30 minutes, decreased to 79 mg/dL at 60 minutes, increased again to 129 mg/dL at 90 minutes, gradually decreased thereafter, and then reached the lowest value (76mg/dL) at 5 hours (Table 1-B). Her serum insulin concentration increased to 29.9μU/mL 30 minutes after loading, declined to 2.1μU/mL as blood glucose levels decreased at 60 minutes, and increased again to 37.0μU/mL at 90 minutes. These results demonstrated that exaggerated insulin secretion occurred in two phases. It was divided into an early stage (within half an hour) and late stage (between 90 min. and 120 min after consuming a meal). She complained discomfort and nausea one hour after loading. Between one and three hours, the patient appeared confused, and she could not recall these hours when she came back. She had a strong desire to eat sweets 4 hours later. These were similar to daily postprandial symptoms. The diagnosis of postprandial syndrome is generally based on reproducing the patient's hypoglycemic symptoms in association with a blood glucose level of less than 50mg/dL (2.8mmol/L) after an OGTT [9]. In the present case, blood glucose levels at 60 minutes in OGTT were 52mg/dL at the previous clinic and 79mg/dL at our hospital. These results did not strictly meet the criteria of postprandial syndrome described above [9].

No treatment is currently established treatment for reactive hypoglycemia with mild adrenal insufficiency. In general, the correction of unbalanced eating habits should be considered prior to administration of the drug. Before thinking to adrenal insufficiency, the dietary approach should be considered as the first treatment of the postprandial reactive

hypoglycaemia. It is important to see a home weighed food diary for a week or to perform dietary instructions by an external guidance. The decrease of intake of non-starchy vegetables and grain fibre might cause the exaggerated insulin excretion after a meal. The attention disorder makes education difficult. These subjects closely depend on relatives and human environment. We attempted changes in her diet and drug therapy to avoid hypoglycemic symptoms after meals. She was recommended to consume small meals every three hours, eat high-fiber food (e.g. between 500 and 1000 grams of non-starchy vegetables per day), have snacks if necessary, and take medicine such as alpha-glucosidase inhibitors [10] to suppress a sharp rise in blood sugar levels after meals. Unfortunately, she did not have the will or motivation to continue the diet therapy. Her mild postprandial hypoglycemia-like symptoms persisted after she was discharged from our hospital.

3. DISCUSSION

Hypoglycemia is uncommon in patients without an underlying illness such as diabetes mellitus. Although rare, hypoglycemia has been reported in people who appear to be healthy with fasting or postprandial timing. Approximately 10 percent of the population has a blood glucose value less than 50mg/dL, but do not show any symptoms of hypoglycemia [5]. A single point measurement of a low plasma glucose concentration does not suggest the presence of a hypoglycemic disorder in a non-diabetic patient. Therefore, in order to diagnose a hypoglycemic disorder, it is important not only to measure the plasma glucose concentration, but also to reproduce the symptoms of hypoglycemia in the course of the OGTT or routine clinical practice. In the present case, the OGTT on admission was extended to 5 hours to determine whether hypoglycemia would occur.

The symptoms of hypoglycemia are nonspecific. The presence of postprandial sympathoadrenal symptoms such as anxiety, weakness, tremors, perspiration, or palpitations is highly suggestive of postprandial hypoglycemia when the glucose concentration is simultaneously low. Three signs, referred to as Whipple's triad, are required in order to diagnose a hypoglycemic disorder. Whipple's triad includes the following: 1) symptoms consistent with hypoglycemia, 2) a low plasma glucose concentration measured with a precise method (not a home glucose monitor) when symptoms are present, 3) the amelioration of these symptoms after the plasma glucose level is raised [11,12].

The diagnosis of postprandial or reactive hypoglycemia is based on reproducing the patient's hypoglycemia symptoms with a blood glucose value less than 50mg/dl during an oral glucose tolerance test [9]. However, this criterion is not sufficiently credible because at least 10 percent of normal subjects have a nadir blood glucose concentration of less than 50mg/dl during a four-to-six-hour OGTT [5], and no correlation has been reported between blood glucose concentrations and the occurrence of symptoms during the test [13]. Therefore, for diagnosis of postprandial hypoglycemia a mixed meal diagnostic test is recommended based on evidence by several studies [14,15]. However, a test meal A [16], which is developed by Japan Diabetes Society and seems to be approximately equivalent to a mixed meal, is used only in some facilities and not yet widely available in Japan. Therefore, a test meal tolerance test is not routinely used compared to OGTT. In our case, she has developed the highly-reproducible symptoms of postprandial hypoglycemia under normal dietary conditions, although the blood glucose levels at that time were not necessarily low blood glucose levels. For these reasons, we clinically diagnosed her symptoms with postprandial hypoglycemia by reference to the test results of OGTT.

Previous studies reported that physiological hyperinsulinemia enhanced epinephrine, norepinephrine, and cortisol secretion as a counter-regulation against hypoglycemia, but did not enhance the secretion of growth hormones or glucagon [17,18]. The results of the 75g OGTT in this case suggested that reactive hypoglycemia was caused by a decrease in cortisol secretion as a counter-regulation against the excessive secretion of insulin; however, serum cortisol concentrations were not examined during the 75g OGTT.

She had been taken to hospital by ambulance due to hypoglycemic-impaired consciousness for three times before she presented to us. However, her daily hypoglycemia-like symptoms were not always accompanied by extremely low levels of blood glucose. Her symptoms had improved in most situations by eating sweets. Previous studies reported that when plasma glucose was measured in patients with postprandial sympathoadrenal symptoms

[19,20,21,22], glucose concentrations were almost invariably normal, and most patients with these symptoms after meals had some types of psychoneurosis on further examination [13,23]. ADHD is generally a condition that causes inattention, hyperactivity, impulsivity, or a combination of all three in children. In this case, she was diagnosed with ADHD at 14 years old, and had attention problems and an impulsive character.

The increase in weight suggests good cortisol production. In the present case, she gained 3kg over three months before admission. It is generally known that extremely low secretory ability of cortisol in patients with primary adrenal insufficiency, or so called Addison's disease, causes weight loss. However, it may not become evident until adrenal insufficiency is advanced [24]. It is because, in general, the symptoms and signs of adrenal insufficiency depend upon the extent of loss of adrenal function such as glucocorticoid production, or whether mineralocorticoid production is preserved. The degree of various stresses also influences the symptoms. On the other hand, insulin mainly enhances glucose uptake by cells such as skeletal muscles and adipocytes, where glucose turns into fat if unconsumed. Therefore, weight gain is common in patients with the excessive insulin secretion, for example the early staged type 2 diabetes mellitus. Considering these, we speculated that her high calorie diet, low activity level and postprandial exaggerated insulin secretion exceed mild adrenal dysfunction, resulting in mild weight gain.

Recent studies reported that low or low to normal early morning cortisol levels were observed in patients with a history of stress-related health changes such as recurrent gastrointestinal symptoms, fatigue, or lassitude. They may have latent primary adrenal insufficiency [25]. Nishikawa et al. advocated a sequential protocol for the screening and definitive diagnosis of subclinical and latent primary adrenal insufficiency. They suggested that the possibility of latent primary adrenal insufficiency should be examined if basal cortisol levels in the morning were less than 11.0 μg/dL [25,26]. Erturk E et al. reported that basal morning serum cortisol values less than 5μg/dL had almost 100 percent specificity, but only 36 percent sensitivity [27]. In this case, her basal cortisol level was 6.0μg/dL. It was not only less than 11.0μg/dL, but close to 5μg/dL, and the possibility of latent primary adrenal insufficiency was strongly suspected.

Table 1-A. The 75g OGTT performed at a previous clinic

	Baseline values (fasting)	30 min.	60 min.	120 min.
Blood glucose (mg/dL)	72	89	52	64
IRI (μU/ml)	3.0	62.6	8.9	11.9

After a 10-hr overnight fast, she ingested a solution containing 75g dextrose, and venous blood samples were obtained at 0, 30, 60, and 120 min in order to determine plasma glucose and plasma insulin.

Table 1-B. The 75g OGTT performed after her admission

	Baseline values (fasting)	30 min.	60 min.	90 min.	120 min.	180 min.	240 min.	300 min.
Blood glucose (mg/dL)	81	124	79	129	118	87	85	76
IRI (μU/mL)	2.6	29.9	2.1	37.0	43.1	16.3	5.9	0.9
Serum CPR (ng/mL)	0.9	8.3	2.9	5.2	6.7	4.8		

Her venous blood samples were obtained at 0, 30, 60, 90, 120, 180, 240, and 300 min in order to determine plasma glucose, plasma insulin, and serum CPR.

Her blood glucose level at 60min dropped sharply due to the excessive secretion of insulin after OGTT. Her blood glucose level at 300 min then dropped again due to the excessive secretion of insulin for the second time. IRI; immunoreactive insulin

CPR; C peptide immunoreactivity

Table 2-A. Diurnal variation of ACTH

	8:00	16:00	23:00
ACTH (pg/mL)	38.7	23.6	3.6
Cortisol (μg/dL)	6.0	4.2	0.6

Blood concentrations of ACTH and cortisol have circadian rhythms, whereas serum cortisol concentrations in the morning were low, as described in the text.

Table 2-B. Rapid ACTH stimulation test

(min)	0	30	60
Cortisol (μg/dL)	6.2	13.2	16.6

Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) associated with hyperinsulinemic hypoglycemia is a very rare entity, but it must be considered as a differential diagnosis of postprandial hypoglycemia. In small series and case reports, NIPHS has clinical features of a male dominance (70%), postprandial hypoglycemia, neuroglycopenic symptoms, and a history of upper gastrointestinal surgery in 40% of the patients (not gastric bypass) [28,29,30,31]. Radiological localization studies such as transabdominal ultrasonography, abdominal CT and celiac axis angiography are negative. The histologic findings show beta cell hypertrophy with enlarged and hyperchromatic nuclei, and increased periductal islets in the pancreas [31,32]. In the present case, there were no abnormal findings in transabdominal ultrasonography and abdominal CT. A selective arterial calcium stimulation test (SACST) with hepatic venous sampling should be performed to establish that hyperinsulinemia was originated in the pancreas [32]. However, in the light of the low prevalence rate of NIPHS and insufficient reaction of the adrenal cortical hormone as a counter-hormone against hypoglycemia, we speculated that the mild adrenal insufficiency was the most likely underlying cause of this case, and did not perform the invasive management such as SACST and pancreatectomy.

Adrenal insufficiency is an uncommon clinical disorder that can be confirmed based on inadequate basal or stress levels of serum cortisol by special stimulation tests. The signs and symptoms of adrenal insufficiency include: fatigue, body aches, unexplained weight loss, low blood pressure, lightheadedness, and loss of body hair. Since the presentation of mild adrenal insufficiency is often insidious and difficult to recognize, careful examinations are required to prevent delays in diagnosing this condition [33,34].

The word “adrenal fatigue” is a collective term of nonspecific symptoms, such as body aches, fatigue, nervousness, sleep disturbances, and digestive problems. It has frequently been references in popular health books and on alternative medicine websites. However, the word “adrenal fatigue” is not currently accepted as a medical term. An advocator of the diagnosis of adrenal fatigue claims it as a mild form of adrenal insufficiency caused by chronic stress such as long-term mental and physical stress. In addition, the symptoms of adrenal fatigue appear to be more indefinite than those of typical adrenal insufficiency.

Unproven theories have been suggested to explain the symptoms of adrenal fatigue. The function of patients’ adrenal glands may be too weak to supply adequate amounts of cortisol against various kinds of emotional, psychological, or physical stress. Therefore, they are likely to exhibit various degrees of adrenal fatigue [4]. However, currently available blood tests are not sensitive enough to detect such a small decline in adrenal function, and results do not appear to support this theory.

The concept of a normal range of laboratory tests is commonly based on a population of so-called “healthy” people. Most laboratory tests are designed to check on a state or sign of a disease. Adrenal fatigue itself is generally not considered to be a disease. In addition, there has never been a reliable urine or blood test to check for or definitively diagnose mild forms of adrenal insufficiency. Therefore, the fundamental problem in using these tests to diagnose adrenal fatigue is that these “healthy” people have never been screened for mild to moderate adrenal dysfunction, only for severe adrenal dysfunction, i.e. Addison’s disease.

Three issues have been associated with hormone measurement. First, the normal range of the plasma levels of most hormones is very broad. It is still “normal” by definition even if the plasma levels are found to be a half or double the individual’s average values, but within the so-called normal range [4,35]. The second issue is the forms of existence of the hormones in the blood. The majority of cortisol circulates bound

to cortisol-binding globulin (CBG-transcortin) and albumin. The unbound form (free), which is the physiologically active form, is normally less than 5% of circulating cortisol [8]. Blood tests to measure the levels of adrenal hormones can only detect hormones levels circulating in the blood, but cannot reveal those inside the tissues or potentially available to the tissues. Thirdly, many steroid hormones, such as cortisol and aldosterone, have notable hormonal fluctuations at various times of the day. Stress also significantly affects adrenal hormone levels. Taken together, it is difficult for untrained doctors to interpret serum cortisol values on current laboratory tests in order to diagnose mild adrenal insufficiency.

Cortisol, the main glucocorticoid that represents 75%-90% of the plasma corticoids, plays a central role in glucose metabolism and in the body's response to various stresses [8]. Patients with adrenal fatigue frequently have erratic or abnormal blood glucose levels in the form of hypoglycemia. They should eat a nutritious snack between 2:00 and 3:00 p.m. to sustain normal blood glucose level because a drop in cortisol levels typically occurs between 3:00 and 4:00 p.m. [4]. In the present case, she had hypoglycemia-like symptoms at that time, and had the urge to eat sweets right away. The test results and clinical manifestations were similar to a state called adrenal fatigue. Based on these results, we diagnosed her with reactive hypoglycemia associated with mild adrenal dysfunction, so-called adrenal fatigue

4. CONCLUSION

In the present case, we speculated that reactive hypoglycemic symptoms may be caused by the mildly decreased secretion of an adrenal cortical hormone as a counter-regulatory hormone against the excessive secretion of insulin after a meal. The results of laboratory examinations and her clinical manifestations were similar to a state called adrenal fatigue. Adrenal fatigue is not currently a medical term, and its entity is not broadly known. Furthermore, abnormalities in her test results were too slight to make a diagnosis of adrenal fatigue. These factors likely led to a delay in diagnosing the condition and inappropriate treatment. We here described an educative case of reactive hypoglycemia associated with so-called adrenal fatigue, and recommended a thorough examination.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying data.

ETHICAL APPROVAL

All necessary ethical approval has obtained from the ethical committee of our hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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