CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
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Carnitine Deficiency and Severe Hypoglycemia Associated with Valproic Acid

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Received November 12, 2012 / Accepted November 14, 2012 / Published December 21, 2012

We present a case of hypoglycemia that is closely related to possible carnitine deficiency during valproic acid (VPA) treatment. A 59-year-old male inpatient with schizophrenia had been successfully treated with long-term administration of risperidone (RIS) 2 mg/day and VPA 900 mg/day for more than 3 years. However, over these 3 years, his body weight gradually decreased (-7.6 kg) and his body mass index (BMI) decreased from 20.3 to 17.3. He experienced an attack of unconsciousness early in the morning, and his blood glucose level at the time was 21 mg/dL. A bolus injection of 20 mL 50% glucose was administered intravenously and he rapidly regained consciousness. Table 1 shows his laboratory results at the time of unconsciousness. The decreased HbA1C level was suggestive of chronically low blood glucose. The decreased serum insulin and C peptide levels might have resulted from compensatory inhibition of insulin secretion due to chronic hypoglycemia. Hypoalbuminemia, hypocholesterolemia, and mild anemia indicated a state of hypoalimentation. Neither hepatic impairment nor an elevated ammonia level was observed. Although the patient exhibited a reduced appetite, he consumed about two-thirds of the hospital meals provided, meaning his food intake was about 1,200 KCal/day. However, he experienced repeated hypoglycemic attacks before meals, and he was therefore transferred to a university hospital for examination. Hormone loading tests (TRH, CRH, LHRH), MRI of the pituitary gland, and whole body CT, including the pancreas, revealed no abnormal findings. The patient was given a diagnosis of unexplained hypoglycemia associated with being thin.

His subsequent blood glucose levels early in the morning were within a range of 30 to 50 mg/dL, with urinary ketone bodies negative, which led to a diagnosis of impaired fatty acid metabolism due to VPA-induced carnitine deficiency. Because carnitine cannot be measured in the clinical setting, carnitine replacement therapy was initiated after obtaining informed consent. In the second week after the start of treatment with levocarnitine 900 mg/day, early-morning stable blood glucose levels of 70 to 90 mg/dL were achieved, with no hypoglycemic attacks, even though the patient continued to be treated with RIS 2 mg/day and VPA 900 mg/day. The patient's appetite gradually increased, and his BMI increased to 19.2 within 6 months after the start of carnitine supplementation.

Carnitine is an essential amino acid necessary for the β-oxidation of fatty acids and energy production in mitochondria. Recent evidence supports a role for the voltage-dependent anion channel in the transport of acyl-CoAs through the mitochondrial outer membrane [1]. On the other hand, VPA is a simple fatty acid and a substrate for the fatty acid β-oxidation pathway. When valproyl CoA is incorporated into mitochondria in the process of VPA metabolism, VPA binds to carnitine, increasing its excretion [2]. It has therefore been hypothesized that VPA may induce carnitine deficiency and cause nonspecific symptoms of deficiency, such as general malaise, hepatotoxicity, and hypoglycemia. Previous data have suggested that some adverse events of VPA may be provoked by carnitine deficiency and the inhibition of mitochondrial β-oxidation [3]. However, VPA monotherapy does not result in a decrease in free carnitine or in the accumulation of long-chain acylcarnitines [1].

Carnitine is obtained in food (animal protein) and is also synthesized in small quantities from trimethyl-

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lysine [4][5]. The plasma carnitine concentration positively correlates with the dietary intake of carnitine [4]. The required daily intake of carnitine is about 10-20 mg, and more than 1,000 times as much is stored in the body, precluding acute deficiency [5]. However, hypoglycemia due to carnitine deficiency in the long-term use of pivalate-conjugated antibiotics has been reported in children [6]. Carnitine levels in humans are reported to vary depending on body composition, diet, and the use of drugs such as pivalate-conjugated antibiotics and VPA [1][4][5][6]. The cause of carnitine deficiency in this patient might have been a combination of increased consumption (VPA metabolism) and decreased storage (lean body). Carnitine deficiency has been believed to result in hyperammonemia. In general, a significant inverse relationship has been found between plasma carnitine and blood ammonia levels [3]. In this case, however, the ammonia level was rather low. One possible reason for the hypoammonemia is that the production of ammonia was decreased due to the patient's lean physique.

Hypoglycemia is one of the severe complications of carnitine deficiency, and is sometimes fatal [6]. The onset of hypoglycemia in the presence of carnitine deficiency may involve an unknown mechanism. According to one theory that has been proposed for the mechanism of hypoglycemia in patients with carnitine deficiency, the inhibition of β-oxidation of mitochondria stimulates the consumption of glucose. Specifically, metabolism cycles daily between fed and fasted states. In the anabolic (fed) state, the liver stores glucose as glycogen, and fatty acid synthesis is active. In the catabolic (fasted) state, the liver becomes a glucose producer, lipogenesis is slowed, and fatty acid oxidation (ketogenesis) is activated. The rate-limiting step for ketogenesis is vested in the carnitine/carnitine palmitoyltransferase system [7]. Thus, when β-oxidation of fatty acids is inhibited by carnitine deficiency, hepatic gluconeogenesis during fasting is decreased, resulting in hypoketotic hypoglycemia.

Another possible mechanism of hypoglycemia is low orexin level-related carnitine deficiency that results in anorexia. In an animal experiment using juvenile visceral steatosis (JVS) mice, which are a model for systemic carnitine deficiency because of a defect of the organic cation transporter (OCTN2), the suppression of the expression of orexin in the hypothalamus may be involved in anorexia, which eventually leads to death from hypoglycemia [8].

More attention should be paid in psychiatric practice to the risk of hypoglycemia due to VPA-induced carnitine deficiency, for which carnitine supplementation might be beneficial.

Table 1. Laboratory data at the time of loss of consciousness

Laboratory parameters	Reference values	Patient's values	Laboratory parameters	Reference values	Patient's values
FBS	70–110 mg/dl	21	γGTP	5–73 IU/I	4
IRI	5-14 mcu/ml	1.0	T-Bil	0.2–1.1 mg/dl	0.3
C peptide	1.1-3.3 ng/ml	0.5	Ammonia	30-86 μg/dl	25
HbA1C (NGSP)	4.6%–6.2%	4.1	BUN	8–20 mg/dl	14.5
Amy	18–57 IU/I	20	Cre	0.3–1.1 mg/dl	0.53
CK	50–240 IU/I	69	UA	3–6 mg/dl	3.4
TP	6.5–8.3 g/dl	6.7	K	3.5–4.9 mEq/l	4.7
Alb	3.7–5.3 g/dl	2.0	Na	135–147 mEq/l	128
Che	185-431 IU/l	133	Cl	98–108 mEq/l	94
T.Cho	130–220 mg/dl	90	WBC	4000–8000/mm^3	7800
TG	50–149 mg/dl	36	RBC	400–530*10^4/mm^3	321
HDL-C	40–86 mg/dl	32	Hb	12–16 g/dl	9.7
LDL-C	70–139 mg/dl	54	Plt	14–37*10^4/mm^3	7.1
LDH	106–211 IU/l	179	VPA	50-100 μg/ml	75.4
AST	8–40 IU/I	33			
ALT	5–40 IU/I	13	U-KB	-	-

Abbreviations: FBS, fasting blood sugar; IRI, immunoreactive insulin; HbA1C, hemoglobin A1C; Amy, amylase; CK, creatinine kinase; TP, total protein; Alb, albumin; Che, cholinesterase; T.Cho, total cholesterol; TG, triglyceride; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase; γGTP, γ-glutamyl transpeptidase; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cre, creatinine; UA, uric acid; K, potassium; Na, sodium; Cl, chloride; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Plt, platelets; VPA, serum concentration of valproic acid; U-KB, urine ketone bodies.

DISCLOSURE

The author declares no conflicts of interest.

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