CASE REPORT

HYPOTHERMIA WITH ACUTE RENAL FAILURE IN A PATIENT SUFFERING FROM DIABETIC NEPHROPATHY AND MALNUTRITION

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SUMMARY - We report a rare case of hypothermia with acute renal failure in a patient suffering from diabetic nephropathy. A 71-year-old male who had been receiving insulin therapy for the treatment of diabetes mellitus complicated with advanced diabetic nephropathy since 1998 was malnourished with an extremely decreased muscle mass. Without any prolonged exposure to excessively low external temperatures or hypothyroidism, pituitary insufficiency, adrenal insufficiency, sepsis, hypoglycemia, and diabetic ketoacidosis, acute hypothermia appeared together with an aggravation of diabetic nephropathy. His skin temperature fell to below measurable levels and his rectal temperature fell to 30.0°C. His consciousness was drowsy and the hypothermia was not accompanied by shivering. Skeletal muscle is known to play an important role as a center of heat production and shivering thermogenesis in skeletal muscle mainly operates on acute cold stress. Therefore, in this case, hypothermia may have occurred because the shivering thermogenesis could not fully act on the acute cold stress due to the dramatically reduced muscle mass. We should always keep in mind that older, malnourished diabetic patients can easily suffer from impairments of the thermoregulatory system.

Key-words: hypothermia, diabetes, renal failure, diabetic nephropathy, malnutrition.

RÉSUMÉ - Hypothermie et insuffisance rénale chez un patient atteint de nèphropathie diabétique et de malnutrition

Nous rapportons un cas clinique, rare, d'hypothermie chez un patient atteint d'une insuffisance rénale consécutive à une nèphropathie diabétique. Un sujet masculin âgé de 71 ans, diabétique, insulinotraité, était porteur d'une nèphropathie diabétique sévère depuis 2 années avec malnutrition et perte massive de la masse musculaire. Sans exposition au froid, ni hypothyroïdie, insuffisance rénale ou surrénalienne, état septique ou acidocétose diabétique, une hypothermie aiguë est apparue en même temps qu'une aggravation de la nèphropathie diabétique. La température cutanée s'est abaissée à un niveau ne permettant plus sa mesure et la température rectale a atteint 30°C. Le patient était somnolent et son hypothermie ne s'accompagnait pas de frisson. Le muscle squelettique joue un rôle déterminant dans la production de chaleur et les tremblements musculaires sont principalement impliqués au cours d'un stress hypothermique aiguë. Nous faisons l'hypothèse que la réduction massive de la masse musculaire a empêché que la thermogenèse par tremblements musculaires ne se produise. Des troubles profonds de la thermorégulation peuvent donc être rencontrés chez des patients diabétiques âgés et malnutris.

Mots-clés : hypothermie, diabète, insuffisance rénale, nèphropathie diabétique, malnutrition.
A 71-year-old male who had been receiving insulin therapy for the treatment of diabetic mellitus complicated with advanced diabetic nephropathy since 1998 was admitted to our hospital because of appetite loss and a high-grade fever. He had also been under drug treatment for neurogenic bladder and prostate hypertrophy. On physical examination he was cachexic, febrile (38.5°C), and malnourished with decreased muscle mass (body mass index: 17.7). Laboratory examinations revealed normocytic anemia (hemoglobin 8.2 g/dl), mild leukocytosis (white blood count 10.5 × 10⁹/l), elevated levels of C-reactive protein (6.3 mg/dl) and serum creatinine (1.6 mg/dl), a reduced plasma protein concentration (4.9 g/dl), and a reduced glomerular filtration rate (24 ml/min). X-ray radiography of the chest showed mild pleural effusion in the left lung field but no pneumonia. Urine was cloudy and Escherichia coli was observed in the urine culture, so he was diagnosed with a urinary tract infection and started on antibiotics. Five days after beginning the treatment, the urinary tract infection showed improvement and the patient’s condition stabilized. Two weeks later, however, acute hypothermia appeared together with a aggravation of the serum creatinine level. His skin temperature fell to below measurable levels and his rectal temperature fell to 30.0°C. No abnormalities were detected in the thyroid, pituitary, and adrenal hormone levels measured at the time of this severe hypothermia. On physical examination at this time he appeared bradycardic and hypotensive, but there was no sign of arrhythmia with J wave. His consciousness was drowsy and hypothermia was not accompanied by shivering. The previous antihypertensive treatment (amlodipine besilate: 5 mg/day and furosemide: 40 mg/day) had been discontinued on occasion of this acute hypothermia. Treatment with oxygenation, external rewarming by heated blankets, and warmed glucose in saline infusions was initiated. During hemodialysis performed to alleviate oliguria and progressive elevation of the serum creatinine level (max 4.4 mg/dl), the patient’s hypothermia and renal dysfunction dramatically improved.

### DISCUSSION

The central thermostat in man is located in the hypothalamus and is controlled by a heat consumption center in the anterior hypothalamus and a heat production center in the posterior hypothalamus. When man is exposed to cold stress, the stimulus is transmitted from peripheral cold-sensitive nerves to the posterior hypothalamus, the sympathetic nerve is activated, and thyrotropin-releasing hormone (TRH) and corticotropic-releasing factor (CRF) secreted through the alpha-adrenergic pathway from the hypothalamus induce the secretion of the thyroid and adrenocortical hormones from the pituitary gland. Because these hormones act as stress hormones, heat is produced by an increased thermogenesis in muscle and adipose tissue. Moreover, when epinephrine is secreted from the adrenal medulla through alpha-adrenergic signals, peripheral vasoconstriction and involuntary constriction of the skeletal muscles (shivering) are induced as means to increase the metabolic rate in a cold environment. All these mechanisms are defense responses against cold-stress. Thus, whenever this system is defective, the body response against hypothermia declines.

Hypothermia is a well-known complication of cold exposure that is frequently reported during the winter months. The condition has also been found in association with hypothyroidism, pituitary insufficiency, adrenal insufficiency, sepsis, hypoglycemia, and diabetic ketoacidosis [1]. Until now, however, there has been no report of severe hypothermia appearing without prolonged exposure to excessively low external temperatures or any of these associated diseases. We report here a very rare case of hypothermia that appeared with the aggravation of diabetic nephropathy.

Under normal conditions, the body temperature is precisely controlled by a central thermostat in the hypothalamus. The appearance of morbid hypothermia without a protracted exposure to cold is rare. Our case is the only reported case of hypothermia appearing in the absence of any associated disease.

Cryogenic substance (endogenous cryogen) has been reported to induce falls in the body temperature accompanied by peripheral vasodilation and suppression of the shivering metabolism. In patients with end-stage renal failure, this decline in temperature has been reported to improve when endogenous cryogen is removed by hemodialysis [2]. Accordingly, hypothermia may be a frequent outcome when acute renal failure (ARF) disrupts the clearance of this substance. In this case, while the etiology of ARF is unknown, dehydration with diuretics may have been involved in the functional ARF.

In contrast, skeletal muscle is known to play an important role as a center of heat production. Extreme decreases in muscle mass lead not only to low basal metabolic heat production but also to an expansion of the relative body surface area. With relatively more skin exposed, conductive, convective, radiant, and evaporative losses of heat from the skin are increased [1, 3]. However, since hypothermia generally does not occur in cases suffering from acute renal failure alone, it is difficult to attribute the condition solely to endogenous cryogen. In our case, the extreme decrease in muscle mass was likely to be an important co-factor contributing to the hypothermic condition.

The thermoregulatory responses to cold exposure are mediated by the shivering of skeletal muscle and the non-shivering of brown adipose tissue (BAT). Recent reports revealed that mitochondrial uncoupling proteins (UCPs) play an important role as mediators
of non-shivering thermogenesis. According to these reports, UCP-1 is exclusively expressed in BAT, UCP-2 is widely expressed throughout the body, and UCP-3 is predominantly expressed in skeletal muscle [4-6]. Furthermore, it has recently been reported that UCP-1 mRNA is exclusively upregulated by cold stress [7], while UCP-2 and UCP-3 mRNA are up-regulated by fasting, exercise training, and thyroid hormone [8]. While this may indicate a link between upregulation of UCP-3 expression and the increase in basal metabolic rate in hyperthyroidism, there has been no evidence confirming a correlation between cold stress and UCP-3. Although non-shivering thermogenesis in BAT in response to cold exposure is known to relate to UCP-1 expression, UCP-1 is far scarcer in human adults than in neonates, and shivering thermogenesis in skeletal muscle mainly operates on acute cold stress. Therefore, in this case, hypothermia may have occurred because shivering thermogenesis could not fully act on acute cold stress due to the dramatically reduced muscle mass.

We should always keep in mind that older, malnourished diabetic patients can easily suffer from impairments of the thermoregulatory system.

REFERENCES