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Original communication

Postmortem biochemistry in suspected starvation-induced ketoacidosis

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ABSTRACT

Significantly increased blood ketone body levels can be occasionally observed in the forensic setting in situations other than exposure to cold, diabetic or alcoholic ketoacidosis. Though infrequent, these cases do occur and deserve thorough evaluation in order to establish appropriate differential diagnoses and quantify the role that hyperketonemia may play in the death process. Starvation ketoacidosis is a rare cause of metabolic acidosis and is a phenomenon that occurs normally during fasting, as the body switches from carbohydrate to lipid energy sources. The levels of ketonemia in starvation ketoacidosis is usually mild in comparison to those seen in diabetic or alcoholic ketoacidosis. In the clinical setting, several cases of starvation-induced ketoacidosis mainly associated with gastric banding, pregnancy, malnutrition and low-carbohydrate diets have been reported. However, starvation ketosis causing severe metabolic acidosis has been rarely described in the medical literature. In the realm of forensic pathology, starvation-induced hyperketonemia has been rarely described. In this paper we present the postmortem biochemical results observed in situations of suspected starvation-induced hyperketonemia that underwent medico-legal examination. In all these cases, the diagnosis of starvation induced-hyperketonemia and the subsequent ketoacidosis was established per exclusionem based on all post-mortem investigation findings. A review of the literature pertaining to the clinical diagnosis of starvation ketoacidosis is also provided.

1. Introduction

Apart from uncontrolled diabetes mellitus, pathologists occasionally encounter other conditions characterized by increased blood ketone body levels. These mainly include hypothermia fatalities (especially in cases without ethanol in blood) and alcoholic-ketoacidosis as well as uncommon cases of intoxication (salicylate, isoniazid and a few other compounds). Hyperketonemia caused by inborn errors of metabolism is exceptional in the forensic setting.[1]

Exposure to cold is characterized by significant stress reactions that stimulate release of counter-regulatory hormones. Enhanced fat catabolism and increased acetoacetate/beta-hydroxybutyrate production are the metabolic consequences of hypothermia-induced secretion of insulin antagonist hormones.[2]

Alcoholic ketoacidosis might occur in non-diabetic, chronic ethanol abusers. In typical cases, the onset of alcoholic ketoacidosis is preceded by prolonged, massive ethanol intake abruptly terminated some days prior due to nausea, vomiting and abdominal pain, often induced by gastritis and pancreatitis. This common presenting feature of vomiting is probably the result of ethanol-induced esophagitis or gastritis and may inhibit all or most food and fluid intake, in some cases for several days, leading to acute starvation. Increased blood acetoacetate/beta-hydroxybutyrate levels in alcoholic ketoacidosis have various causes. Ethanol oxidation is responsible for enhanced production. Dehydration and volume contraction impair ketone body excretion by the kidneys, leading to further elevation in blood levels. Lastly, various hormonal changes mediate depletion of hepatic glycogen store

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and increased mobilization of free fatty acids from adipose tissue to the liver, with subsequent increased ketone body synthesis.[3–6]

In addition to the aforementioned conditions, acute prolonged starvation and ketogenic diets may be responsible for hyperketonemia and metabolic acidosis, though less frequently. Starvation-induced hyperketonemia involves carbohydrate depletion with free fatty acid mobilization. During fasting, glycogenolysis and gluconeogenesis offset potential hypoglycemia and are accompanied by lipolysis and production of ketoacids (acetoacetate and beta-hydroxybutyrate), which provide an alternative fuel source, decreasing glucose utilization by the brain. The associated ketosis and metabolic acidosis are generally mild and not life threatening, though a number of factors, including exercise and stress, may exacerbate the severity of the metabolic acidosis. Indeed, starvation ketosis causing severe metabolic acidosis is occasionally described in the medical literature and rarely reported in the forensic setting.[1,7,8]

This notwithstanding, significantly increased blood ketone body levels can be sporadically observed in forensic casework in situations other than exposure to cold, diabetic or alcoholic ketoacidosis. Though infrequent, these cases do occur and deserve thorough evaluation in order to establish appropriate differential diagnoses and quantify the role that hyperketonemia may play in the death process.

The paper presented herein focuses on postmortem biochemical investigation results observed in presumptive cases of starvation-induced hyperketonemia that underwent medico-legal examination. In all these cases, the hypothesis of starvation induced-hyperketonemia (and the subsequent ketoacidosis) was formulated *per exclusionem* based on all postmortem investigation findings. A review of the literature pertaining to the clinical diagnosis of starvation ketoacidosis is also provided.

2. Material and methods

The present study was carried out in 2016, concerning medico-legal autopsies performed between 2010 and 2015. A total of 5 cases of suspected starvation induced-hyperketonemia (2 males and 3 females) were retrospectively selected.

The hypothesis of starvation-induced hyperketonemia was formulated in all these cases after reviewing information and data obtained from police reports, medical and social histories, autopsies, histology, toxicology and biochemistry.

All cases originated from forensic practice with deaths occurring outside the hospital. Data pertaining to antemortem biochemical results were therefore unavailable.

Circumstantial elements as well as macroscopic and microscopic results did not suggest exposure to cold or hypothermia as the main or contributing cause death in any of these cases. According to medical information obtained from local health services and practitioners, all cases were not either diabetic or chronic ethanol abusers and did not suffer from hyperthyroidism.

Toxicology and postmortem biochemistry were systematically performed on femoral blood, postmortem serum from femoral blood, vitreous humor, urine, pericardial fluid and hair samples collected at autopsy. In order to confirm or rule out increased ketone levels due to uncontrolled diabetes mellitus, exposure to cold, alcoholic ketoacidosis and severe hyperthyroidism, the following biochemical markers were systematically tested:

- glycated hemoglobin in femoral whole blood,
- glucose in vitreous humor,
- adrenaline and metanephrine in urine,
- ethanol in femoral whole blood,
- urea nitrogen, creatinine and uric acid in postmortem serum from femoral blood,
- total proteins, albumin and pre-albumin in postmortem serum from femoral blood,
- thyroid hormones (tyroxine and triiodothyronine) and thyroglobulin in postmortem serum from femoral blood,
- ethyl glucuronide in hair.

3. Results

Table 1 summarized the main postmortem biochemistry results in the studied subjects.

Body mass indexes ranged from 14.1 to 22.3.

Biochemical investigations revealed increased blood, vitreous, pericardial fluid and urine beta-hydroxybutyrate concentrations, ranging from 1200 to 8800 μm/l (blood), 1150–8600 μm/l (vitreous), 1300–9100 μm/l (pericardial fluid) and 2200–21,600 μm/l (urine).

Drug induced-hyperketonemia by isoniazid, salycilate and other compound ingestion was excluded by toxicology.

Glycated hemoglobin concentrations were normal in all cases. Blood ethanol was undetectable in all subjects. Vitreous glucose levels were systematically lower than 4 mmol/l and confirmed the absence of hyperglycemia at the time of death. Adrenaline and metanephrine values in urine were lower than concentrations usually observed in hypothermia fatalities and fall within postmortem normal ranges. Urea nitrogen, creatinine and uric acid in postmortem serum from femoral blood were all increased in 3 out of 5 cases (case 1, case 2 and case 5), possibly suggesting dehydration and volume contraction due to concomitant decreased fluid intake. Total proteins and albumin were decreased in 3 out of 5 cases (case 1, case 2 and case 5) whereas pre-albumin concentrations were decreased in 4 out of 5 (case 1, case 2, case 4 and case 5), possibly indicating prolonged reduced food intake. Thyroid hormones and thyroglobulin were not increased in any subject. Lastly, ethyl glucuronide determination in hair failed to suggest chronic ethanol intake, thus confirming macroscopic and microscopic findings (Table 1). In 2 out of 5 cases (case 1 and case 3), a cause of death could be identified and measured hyperketonemia was not considered to have played any role in the death process. In the remaining 3 out of 5 cases (case 2, case 4 and case 5), the cause of death could not be identified after all investigations. Starvation ketoacidosis and the underlying hyperketonemia were not considered the main cause of death, though a contributing role was not categorically excluded.

4. Discussion

Ketone bodies (acetoacetate, beta-hydroxybutyrate and acetone) are by-products of fat metabolism and are primarily synthesized as an alternative energy source in some specific situations. The liver contributes acetoacetate and beta-hydroxybutyrate to the blood to supply alternative fuels for extra-hepatic tissues when glucose availability is limited. Both acetoacetate and beta-hydroxybutyrate are acid anions, meaning that increased levels of these compounds result in a drop of blood pH. Once released into the blood, they dissociate to become water-soluble anions and are distributed at different concentrations in the water components of the body. Acetone is a neutral compound, does not participate in energy generation, is of little metabolic significance and, unlike acetoacetate and beta-hydroxybutyrate, does not affect blood bicarbonate concentration, arterial blood gases or pH. It is soluble in both water and lipids, and is either exhaled or excreted. Physiologic ketonemia occurs when hepatic