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Hyperammonemia in Organ Transplant Patients: Pathophysiology and Treatment

Sano Paulson*

Department of Anesthesiology and Resuscitology, Okayama University Hospital, Japan

Hyperammonemia has long been thought to be a hepatic issue, and it is commonly described in the literature as the penultimate step leading to death in patients with liver failure. Inborn defects of urea metabolism, Reye syndrome, pharmaceuticals that disrupt enzymes involved in ammonia metabolism, gastric bypass surgery, and urinary tract infections with urea-splitting organisms are all possible causes of Hyperammonemia. Hyperammonemia is very common in transplant recipients. This is most noticeable in lung transplant recipients, while it has also been observed in other organ transplant recipients. The processes underlying the occurrence of Hyperammonemia in transplant patients are unknown. Solid-organ transplantation is becoming more common in the United States for a variety of clinical conditions. After transplantation, neurologic problems are prevalent, affecting one-third of patients. Hyperammonemia is a rare but deadly complication after a transplant. Ammonia is a strong neurotoxic when levels above 200 mol/L, producing astrocyte enlargement, cerebral edoema, increased intracranial tension, and, in rare cases, cerebral herniation.

Description

Hyperammonemia has become widely recognised as a major post transplantation complication over the last three decades. 4 days after orthotopic lung transplantation, Lichtenstein et al4 described a patient with normal liver function and significant Hyperammonemia. Several case reports and case series have been published since then, with Hyperammonemia being recognised as a serious complication after lung transplantation. The incidence of Hyperammonemia among lung transplant recipients has been reported to be as high as 4%. Despite its rarity, other transplantations, such as liver, bone marrow, kidney, and combination heart-lung, have resulted in Hyperammonemia [1]. An instance of delayed hyperammonemia following islet cell transplantation has also been reported. Hyperammonemia in liver transplant recipients is uncommon and has only been reported in cases of graft failure or residual portosystemic shunting. Patients who get a liver from a donor with ornithine transcarbamylase deficiency have been reported to have hyperammonemia without transplant failure. The most prevalent congenital urea cycle disease, ornithine transcarbamylase deficiency, is an X-linked disorder that primarily affects men [2]. Adult females may be unaware of heterozygous enzyme mutations until the liver is donated and exposed to a stressful environment, such as after transplantation. It has also been seen in a child's liver.

Although cases have been documented months later, hyperammonemia usually appears 5 to 14 days following transplantation. Many patients go unnoticed and present with extremely high ammonia levels later in the course. Some patients have had ammonia levels of over 1,000 mol/L. The cause of more severe hyperammonemia in some people is unknown. About 80% to 90% of patients with hyperammonemia require renal replacement therapy (RRT), which usually involves frequent and long dialysis treatments. In transplant recipients with hyperammonemia, mortality rates of 40% to 75% have been recorded. The maintenance of ammonia homeostasis involves several organs. Plasma ammonia levels in healthy humans are kept within a restricted range. The majority of it resides as an ammonium ion (NH_4^+) at physiological pH, but it diffuses across cell membranes as ammonia gas (NH_3) [3].

The intestinal system produces ammonia, which is then detoxified in the liver and expelled through the kidneys. Ammonia uptake is heavily influenced by skeletal muscle. Ammonia detoxifying ability is low in the brain, which is the primary target of ammonia toxicity. We'll talk about ammonia metabolism and the role of several organ systems in hyperammonemia in this section. Both the small and big bowels produce a lot of ammonia. Through bacterial urease breakdown, dietary protein creates half of the daily ammonia synthesis. The other half is made up of circulating amino acids, primarily glutamine, which is the body's most prevalent free amino acid. In the liver, intestinal ammonia enters the urea cycle and is converted to urea via several important enzymes and bicarbonate. Ammonia detoxification may be affected by changes in acid-base status. The urea cycle is responsible for the majority of hepatic ammonia detoxification. In healthy patients, a remarkable functional hepatic reserve explains why even a three-quarters liver resection is frequently well tolerated and ammonia metabolism is unaffected [4]

Complete urea cycle enzyme deficits are frequently present at birth, resulting in catastrophic neurologic consequences. Partially deficient people may not show symptoms until later in life for unknown reasons, and they're frequently linked to physiologic stressors like pregnancy or disease. The patient presented in the clinical vignette received no formal testing, although it is possible that he had a partial enzyme deficiency that emerged when he was subjected to a stressful situation, such as severe hypothyroidism and acute sickness. The proximal tubule of the kidney is the primary site of ammoniagenesis, with glutamine as the primary substrate. Ammonia can be produced or excreted by the kidneys. Increased ammonia excretion in urine with a net negative ammonia balance occurs in metabolic acidosis, whereas alkalosis has the reverse effect. The alkalemic patient in the clinical vignette had a pH of 7.5, which impaired ammonia excretion. Other factors that regulate ammonia synthesis and excretion include ion transporters, potassium levels, hormones, and urine flow. Potassium deficiency can increase the generation of proximal tubular ammonia [5].

Conflict of Interest

None

***Corresponding author:** Sano Paulson, Department of Anesthesiology and Resuscitology, Okayama University Hospital, Japan, E-mail: Sano.paulson46@gmail.com

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