Refeeding Syndrome: Report of a Case

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Refeeding syndrome is an under diagnosed, but clinically important syndrome, and can be defined as acute electrolyte abnormalities, fluid retention, and dysfunction of various organ systems in malnourished patients undergoing refeeding, whether orally, enteraly, or parenterally. The hallmark biochemical feature of refeeding syndrome is hypophosphatemia. The syndrome almost always develops during the early stages of refeeding. To avoid the development of this potentially lethal condition, nutritional support in patients at risk should be increased gradually over a period of several days while assuring adequate amounts of vitamins and minerals.

Key words: hypophosphatemia, refeeding syndrome

Introduction

Refeeding syndrome is a potentially fatal complication of the nutritional management of severely malnourished patients. Starved or severely malnourished patients can undergo life-threatening fluid and electrolyte shifts following the initiation of aggressive nutritional support therapies. This phenomenon is known as ‘refeeding syndrome’ and can occur in patients receiving oral, enteral, or parenteral nutritional support.

The true incidence of refeeding syndrome is unknown, probably due to the lack of a universally accepted definition. In a study of 10,197 hospitalized patients, the incidence of severe hypophosphatemia was 0.43%, with malnutrition being one of the strongest risk factors1). Studies report a 100% incidence of hypophosphatemia in patients receiving total parenteral nutrition solutions that do not contain phosphorus. When solutions containing phosphate are used, the incidence decreases to 18%2). In a well designed prospective cohort study of a heterogeneous group of patients in intensive care units, 34% of patients experienced hypophosphatemia soon after feeding was started (mean: 1.9 days, standard deviation: 1.1 days)3). We present the case of a starved malnourished patient with liver cirrhosis and upper gastrointestinal bleeding who developed polymorphic ventricular tachycardia (VT) related to severe electrolyte imbalance after parenteral feeding.

Case Report

This 64-year-old man presented with tarry stools of several days’ duration. His medical history included alcohol and hepatitis B virus-related liver cirrhosis and gastric ulcer. This patient had chronic alcoholism for 30 years, with consumption of sorghum liquor of more than 750ml/day, without an
alcohol free period. His height was 172 centimeters and his actual body weight was 50 kilograms. His body mass index was about 17, showing that he was underweight. His subjective global assessment score for nutritional status was C. According to statements by his family, he continued sorghum liquor consumption, but decreased his oral food intake to a minimal amount several days prior to hospital admission.

After admission to the hospital, the patient underwent esophagogastroduodenoscopy, which showed esophageal varices with bleeding and a small gastric ulcer. Initially his consciousness was clear and he was cooperative; his ammonia level was normal. Due to active upper gastrointestinal bleeding, nothing by mouth was given and an intravenous infusion of 5% glucose plus 0.45% sodium chloride solution, at a rate of 60ml/hour, and an intravenous infusion of 60 ml of 50% glucose water every 6 hours. Additionally, 100mg of vitamin B-complex was added to treat probable thiamine deficiency of chronic alcoholism. Nine hours after admission, the patient became agitated and intravenous haloperidol 10mg in 30 minutes was given. Eleven hours after admission, he developed polymorphic VT, which recurred three times within the first 3 days of admission. Although no previous cardiac disease was mentioned, we consulted a cardiovascular specialist who noted new QT prolongation compared to a previous electrocardiogram (ECG) and torsades de pointes was highly suspected. We checked electrolytes levels including potassium, magnesium, calcium, and phosphate. Surprisingly, the patient’s potassium level had decreased from 3.62mEq/L to 2.63mEq/L (normal range: 3.5–5.0mEq/L) and his magnesium level had decreased from 2.18mg/dL to 1.31mg/dL (normal range: 1.9–2.5mg/dL) after glucose water infusion. Severe hypophosphatemia was simultaneously noted, with a phosphate level of 0.8mg/dL (normal range: 2.3–4.7mg/dL). Due to severe hypophosphatemia and worsening hypokalemia and hypomagnesemia after glucose water infusion, aggressive correction of the electrolyte imbalance and withdrawal of haloperidol were suggested by the cardiovascular specialist. In the clinical course of treatment of polymorphic VT, direct cardioversion of 200 joules was performed two times and a lidocaine infusion about 1mg/minute was administered. Because of the malnourished status of this patient and deterioration of hypokalemia and hypomagnesemia after glucose water infusion, both refeeding syndrome related electrolyte imbalances and haloperidol led to the development of polymorphic VT and highly suspected torsades de pointes.

After correction of electrolytes imbalance, tachyarrhythmia disappeared on 4th day after admission. Meanwhile, a series of examinations including electrocardiography, cardiac enzymes, and cardiac echo did not reveal any evidence of ischemic heart disease or cardiomyopathy. He was discharged on day 13 after admission.

**Discussion**

Refeeding syndrome is an under diagnosed but clinically important syndrome characterized by acute electrolyte abnormalities, fluid retention, and dysfunction of various organ systems. It can be defined as severe electrolyte and fluid shifts associated with metabolic abnormalities in starved or malnourished patients undergoing refeeding, whether orally, enterally, or parenterally. Refeeding syndrome is associated with significant morbidity and mortality. Clinical features are fluid-balance abnormalities, abnormal glucose metabolism, hypophosphatemia, hypomagnesemia, and hypokalemia. In addition, thiamine deficiency can occur following the initiation of nutritional support therapies.

Refeeding syndrome was first observed
in the first century by Josephus Flavious who noted an epidemic of deaths among Jews who had been entrapped and starved by the Romans. This historian was able to point out that death occurred among those who engorged themselves, while those who restrained their appetite escaped death. It was also described in Far East prisoners of war after the second world war. Abnormal hemodynamic and fluid physiology were present during the refeeding of war victims in a cachectic state. In the clinical setting, rapid weight gain, severe hypophosphatemia, and heart failure were all reported. Refeeding syndrome has recently become a popular topic in medical literature with the advent of total parenteral nutrition in the 1970s and 1980s for starving and chronically ill patients.

Patients that are very small, very large, or very old and diagnosed with anorexia nervosa, kwashiorkor, marasmus, chronic alcoholism, chronic malnutrition-underfeeding, prolonged intravenous hydration, morbid obesity with massive weight loss, patients underfed for 7–10 days with evidence of stress, depletion and prolonged fasting are at the greatest risk. Crook also stated that oncology patients, hunger strikers, and postoperative patients are also at risk.

Physiologically, throughout a prolonged state of starvation, the secretion of insulin is decreased in response to a reduced intake of carbohydrates. Energy is derived mainly from lipolysis rather than gluconeogenesis, with relative sparing of protein. This results in an intracellular loss of phosphorus, potassium, and magnesium but with normal serum levels. On refeeding with excess glucose-based nutritional regimens, insulin is released into the blood stream and there is a shift from the metabolism of fat to carbohydrate. The substrates required for metabolism of glucose are rapidly consumed. These include potassium and thiamine, which are needed to bring glucose into the cell, and phosphorus and magnesium, which are required for intracellular formation of adenosine triphosphate. Serum levels of phosphate, potassium, and magnesium fall significantly with increased demands. Furthermore, endogenous insulin secretion is stimulated during glucose supply, or insulin must be administered exogenously to maintain normoglycemia. Increased insulin also leads to hypophosphatemia, hypokalemia, and hypomagnesemia. Severe hypophosphatemia, hypomagnesemia, and hypokalemia can result in potentially lethal neurologic and cardiovascular complications.

Phosphorus has numerous roles in the functions of bodily systems. It is crucial for normal function of erythrocytes, leukocytes, platelets, and oxygen liberation from oxy-hemoglobin, ATP synthesis, and normal function of the central nervous system. Additionally, it is a structural component of phospholipids, nucleoproteins, and nucleic acids, and an intermediate in glycolysis and oxidative phosphorylation. Glycolysis produces a byproduct called diphosphoglycerate (2,3-DPG), which acts to regulate the dissociation of oxygen from hemoglobin. A decrease in serum phosphorus levels affects cardiac, neuromuscular, respiratory, and blood cell functions. Life-threatening cardiopulmonary and neurological complications were observed on the refeeding of severely malnourished patients during the Second World War and among patients receiving phosphate-free hyperalimentation containing glucose. Additionally, severe hypophosphatemia accompanied by life-threatening dysfunction is also reported among patients after institution of enteral nutrition. Marik and Bedigian diagnosed hypophosphatemia induced by refeeding in 34% of critically ill patients after initiation of feeding even with a phosphate-supplemented nutritional regimen. Currently, the only risk factor predicting hypophosphatemia is a serum pre-albumin concentration of less than 110g/L.
Magnesium is second to potassium as an intracellular cation and is a cofactor in several enzymatic reactions\(^4\). Potassium is the major cation in the intracellular space. The major physiological roles of potassium include regulation of muscle and nerve excitability, control of intravascular volume, protein synthesis, enzymatic reactions, and carbohydrate metabolism. Among patients requiring refeeding, hypomagnesemia and hypokalemia exacerbate the effects of hypophosphatemia in an already deteriorating body metabolic system. These disturbances in electrolyte metabolism are also accompanied by neuromuscular dysfunction and cardiac arrhythmia.

Our patient developed life-threatening polymorphic VT related to haloperidol and severe electrolyte imbalance due to refeeding syndrome. Polymorphic VT is defined as an unstable ventricular rhythm faster than 100 beats per min with a continuously varying QRS complex morphology in any recorded ECG lead. Polymorphic VT is generally a hemodynamically unstable rhythm, and urgent defibrillation is usually necessary. In addition to immediate cardioversion, further therapy is required to treat the underlying disorders and to prevent recurrence. The specific approach depends upon whether or not the QT interval on the baseline ECG is prolonged. Polymorphic VT that occurs in the setting of QT prolongation is considered as a distinct arrhythmia, called torsades de pointes. Torsades de pointes is a form of polymorphic VT that occurs in the setting of acquired or congenital QT interval prolongation. The most common causes of acquired long QT syndrome (LQTS) are medications and electrolyte disorders particularly hypokalemia or hypomagnesemia. Drugs are a common cause of acquired LQTS and torsades de pointes. The major classes of drugs that prolong the QT interval include certain antipsychotic and antidepressant medications (e.g., haloperidol), antiarrhythmic drugs, certain non-sedating antihistamines, macrolide antibiotics, and certain gastric motility agents. Upon admission, the electrolyte levels of our patient, including potassium and magnesium, were normal; thus, we did not add additional electrolytes. However, polymorphic VT and torsades de pointes developed after parenteral feeding and worsening hypokalemia, hypomagnesemia, and severe hypophosphatemia. Clinicians should be more alert to the possible occurrence of refeeding syndrome in patients requiring refeeding and check electrolytes levels frequently after feeding.

In addition, glucose homeostasis as well as sodium and fluid retention commonly occur with refeeding syndrome. Hyperglycemia can be caused by the infusion of glucose, which then causes dehydration, ketoacidosis, osmotic diuresis, and a hyperosmolar non-ketotic coma\(^7\). Furthermore, carbohydrate administration can enhance carbon dioxide production resulting in an increased respiratory quotient, thereby increasing minute volume and causing dyspnea and even respiratory failure in susceptible patients. Fluid retention is described with expansion of the extracellular space, which results in significant weight gain, edema, volume overload, and acute cardiac failure. Preventing extracellular water expansion during refeeding of severely malnourished patients appears to be of paramount importance. Water and sodium content should be limited and their administration tailored to the individual response in terms of sodium urinary excretion, fluid balance, and weight changes.

Thiamine deficiency is of particular importance with refeeding and especially in patients suffering from chronic alcoholism. Since thiamin is a cofactor in some enzymatic reactions, the demand for thiamin due to an increase in metabolic activity secondary to carbohydrate consumption can decrease the amount of available thiamin\(^7,11\).
Thiamin deficiency can precipitate acute neurological deterioration such as Wernicke’s encephalopathy or Korsakoff’s syndrome and cardiac failure\(^{(12)}\). Thus, thiamine should be given prior to refeeding in severely malnourished patients.

Furthermore, during prolonged starvation, a reduction in protein degradation in muscle and other tissues is the consequence of adaptive metabolic mechanisms. The introduction of excess protein can overload various enzymatic functions. The activity of enzymes of amino-acid metabolism is reduced, which can lead to an increased plasma concentration of amino acids during refeeding. The concentration of amino acids in blood can exceed the capacity of the urea cycle and thus, hyperammonemia can occur. The death of patients with severe malnutrition re-fed with a protein-rich diet has been attributed to this metabolic derangement\(^{(12)}\).

Refeeding syndrome complications can be severe and even fatal. To avoid the development of the refeeding syndrome, nutrition support in patients at risk should be increased slowly while assuring adequate amounts of vitamins and minerals. Meanwhile frequent monitoring of vital signs, electrolytes, including potassium, magnesium, and phosphate, looking for signs of edema, congestive heart failure, and mental status changes are all important during refeeding. However, the amount of recommended energy and macronutrient requirements differ somewhat in the literature\(^{(13-15)}\). Suggested nutritional repletion should started with 10–15 kcal/kg/day\(^{(13,14)}\) to 20 kcal/kg/day\(^{(15)}\) in the first 3 days, slowly increasing to 15–20 kcal/kg/day on day 4 to day 6 if no refeeding problems are encountered, then the number of calories can be increased to 20–30 kcal/kg/day on days 7 to 10. In addition, clinicians should anticipate the additional requirements, particularly of phosphate, potassium, magnesium, and thiamine, and minimize sodium chloride and fluid intake, unless the patient is sodium chloride depleted.

In conclusion, refeeding syndrome may occur more commonly than is recognized in malnourished patients, and can have profound and widespread physiologic effects. It is imperative for clinicians to identify patients at risk and apply appropriate monitoring and supplementation of electrolytes and vitamins to prevent potentially life-threatening complications.

References

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復食症候群：病例報告

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營養不良的病患在重新接受營養補充治療時，無論經由口服、腸道、或靜脈的途徑，有因此而產生急性電解質異常、體液滯留、器官功能失常的風險，這個具有重要性但診斷率不高的臨床表現就稱為復食症候群。低血磷是復食症候群的生化檢驗特徵。一般而言，復食症候群大都發生在病患重新接受營養補充治療的初期。為了避免這個可能致命的潛在危機，針對具有風險的病患，給予營養補充治療時，除了確保已供給足夠的維生素及礦物質之外，營養補充治療宜花費數天的時間做漸進性的調整。

關鍵詞：低血磷，復食症候群

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