Refeeding Syndrome in a Critically Ill Child

Fabíola I. Suano de Souza[1], Heitor Pons Leite[2,*], Walter Jacob Chwals[3] and Werther Brunow de Carvalho[4]

[1]*Discipline of Social Pediatrics, Department of Pediatrics, Federal University of São Paulo, Brazil*

[2]*Discipline of Nutrition and Metabolism, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil*

[3]*Professor of Surgery and Pediatrics, Tufts University School of Medicine, Boston, Massachusetts, USA*

[4]*Instituto da Criança, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil*

Abstract: *Objective*: To report a case of a child interned in an ICU of a University Hospital who developed *refeeding syndrome*, and to review the specific literature pertinent to this area.

Case Report: An eight year-old, previously healthy, male patient was admitted for necrotizing pneumonia. On admission the child had a z-score of weight for height of 0.38 and height for age of -0.74. Following 60 days' hospital admission he had lost 27.5% of initial weight. Enteral tube feeding, with an energy intake equivalent to the basal metabolic rate plus 20% for stress, was initiated and gradually increased during the stabilization phase. After receiving 2000 kcal/day for 5 days, hypophosphatemia was detected in association with an increase in hepatic enzymes and hyperglycemia. No concomitant worsening of the white blood count or evidence of inflammatory activity was present. These alterations were accompanied by an increase in pulse rate and body temperature, thereby leading to a diagnosis of refeeding syndrome. Energy intake decreased to 1520 kcal/day, resulting in a marked improvement of the laboratorial parameters in less than a week.

Conclusions: Refeeding syndrome is a potentially dangerous complication of increased caloric administration in critically ill pediatric patients. Early recognition and appropriate adjustment of nutritional support is important to avoid the serious consequences which may ensue if this condition is left untreated.

Keywords: Malnutrition, enteral nutrition, nutrition support, intensive care unit, critical illness.

INTRODUCTION

Total daily energy requirements in healthy individuals consist of the metabolic basal rate, the energy needed for activities, diet-induced thermogenesis and non voluntary physical activity losses and, in the pediatric age range, the energy for growth and development. The latter are the ideal parameters to assess whether a child is receiving an adequate intake of nutrients. However, these concepts hold true only for healthy children, since when injury induces a metabolic stress response, nutritional requirements can change. Clinical conditions such as sepsis, extensive surgery, or trauma, which trigger the systemic inflammatory response syndrome, induce a cascade of metabolic adaptations which are characteristic of the stress response. As result of this response a sequence of metabolic events is initiated that includes the catabolism of body stores of carbohydrate, fat and protein to provide substrate necessary for surviving. This state results in the loss of endogenous tissue and malnutrition. As the stress response resolves, adaptative anabolic metabolism ensues to restore catabolic losses.

The refeeding syndrome represents a series of metabolic complications which take place during rapid nutrient administration, particularly in malnourished patients. It results in the depletion of intracellular ions, fluid redistribution, vitamin deficiency, increased hepatic enzymes, hyperglycemia, hypertriglyceridemia, cardiac arrhythmia, respiratory failure and, in more severe cases, congestive heart failure [1, 2]. Though it can occur frequently, it is very seldom diagnosed in intensive care unit patients [3, 4].

Children are particularly vulnerable to this condition because they have greater nutrient requirements in comparison to adults [5, 6].

Since reviews on this topic do not discuss critically ill pediatric patients, this report is presented with literature review to improve awareness of this condition in these children.

CASE REPORT

An eight year-old, male patient was admitted to the general pediatric unit with a three-day history of fever, vomiting, and pain in the left hemithorax, which was

*Address correspondence to this author at the Rua Loefgreen 1647, Zip code 04040-032, São Paulo – SP, Brazil; Tel: (5511) 991927326;
Fax: (5511) 50844538; E-mail: heitorpons@gmail.com

E-ISSN: 1929-4247/14 **© 2014 Lifescience Global**

worse on deep inhalation and was accompanied by coughing with yellow secretions. He had been previously healthy with no significant past medical and dietary history or underlying diseases. Chest radiography revealed almost total opacification of the left hemithorax.

On hospital admission z-score height for age (HAZ) stood at -0.74 and weight for height (WHZ) was 0.38, according to WHO standard (normal range from -2 to +2 z-score). Diet history showed no deficiencies of nutrients intake.

With worsening clinical status, the child underwent surgical drainage of a 350 ml empyema and was then transferred to the ICU. During the ICU stay he developed necrotizing pneumonia, acute respiratory distress syndrome, sepsis and multiple organ dysfunction. Thorax CT showed bronchiectasia and pulmonary fibrosis and the patient underwent partial lobotomy of the left lung. Enteral feeding consisting of a polymeric enteral diet at an energy density of 1kcal/ml (Nutren Junior, Nestlé Clinical Nutrition, Vevey-Switzerland) was delivered during the metabolic stress and stabilization phases at a quantity equivalent to the basal metabolic rate (plus stress factor of 1.2) [5] according to the WHO method of estimating basal metabolic rate based on weight, age, and sex: [amount of calories in kcal/kg/day: (22.7 x weight) + 495] [8]. During this stage protein supply was 2 to 2.5 g/kg according to the recommendations for critically ill children [9]. As the patient improved clinically, gradual increases in energy delivery were made to support anabolism.

The initial period of severe infection resulted in substantial loss of 4.5 kg body mass (18.7% weight loss) at 30 days, and 6.6kg (27.5%) at 60 days hospitalization. A z-score weight for height of -3.21, and a cumulative weight loss of 7 kg was consistent with acute malnutrition.

After 2 months hospitalization he had no fever, clinical and laboratory data demonstrated resolution of the infection and serum levels of electrolytes were normal. At that time, aiming at nutritional rehabilitation, enteral feeding was increased from 1500 to 2000 kcal over 5 days. At that point, the child developed hypophosphatemia and an increase in hepatic enzymes (ALT and AST, U/L), without any change in WBC. Serum albumin concentration was 3.8 g/dl, glycemia 209 mg/dl and prothrombin time activity 100%. Serum levels of creatinine, sodium and potassium were normal. Abdominal ultrasound showed hepatomegaly with heterogeneous texture of hepatic parenchyma. These alterations were accompanied by increases in pulse rate (median values/24h 150 min^{-1}, in body temperature (from 36.6 to 37.2 ^{o}C), consistent with a diagnosis of refeeding syndrome. Therefore, caloric intake was reduced by approximately 25% (1520 kcal/day), resulting in median pulse rate of 120 min^{-1} within 24h, normal body temperature, and a noticeable improvement in serum phosphate level (mg/dL) and laboratory tests in less than a week. Energy supply, body weight and relevant biochemical data over the period of feeding are shown in Table **1**.

DISCUSSION

The mechanisms of overfeeding in critically ill children have been mentioned previously [5]. However, a comprehensive review of the refeeding syndrome in critically ill children does not appear in the literature,

Table 1: Body Weight, Protein-Energy Supply, and Biochemical Data Over the Period of Feeding. Refeeding Syndrome Diagnosed on Day 7

Day	1	3	5	6	7	8	10	11	14
Weight (kg)	17.3	18	18	18	18	18	17.4	17.4	18
Energy intake	1920	2000	2000	2000	2000	1520	1520	1520	1520
Carbohydrate (g/kg)	12.2	12.2	12.2	12.2	12.2	9.6	9.6	9.6	9.3
Urea (mg/dL)	40	34		51		52			34
Blood glucose (mg/dL)	130			110	209				94
AST (IU)	35				170				32
ALT (IU)	74				631				146
P (mg/dL)	5.2	3.8			3.1			4.3	5.1
Mg (mg/dL)	1.7	1.4			1.5				1.8

Legend: P – phosphorus (normal range for children 3.8 to 6.5 mg/dL).
At an energy density of 1kcal/mL of the enteral diet, vitamin and mineral needs of children aged 1-10 years can be met with a total intake of 1000 mL.

and the importance of the timely recognition and appropriate treatment of this condition is essential to achieve a successful clinical outcome.

Factors which may predispose to the onset of refeeding syndrome include severe malnutrition, anorexia nervosa, chronic alcoholism, prolonged fasting, intestinal resection (bariatric surgery) and cancer. Since ICU patients frequently experience acute metabolic stress states resulting in significant ponderal loss, they are at particular risk of developing this clinical condition.

In a review of the literature on this subject for the pediatric age group, published reports were found which involved patients under 18 years of age who had developed "refeeding syndrome" while on enteral nutrition. A seriously compromised nutritional state was common to all of these [10]. This review did not include critically ill children. In a recent study conducted in a tertiary pediatric hospital designed to manage high-risk populations 9% of eligible patients were found to be at risk for refeeding syndrome. The most frequent risk profiles were underfeeding or fasting for at least 10 to 14 days and less than 80% of ideal body weight [11].

Our patient developed significant nutritional compromise and ponderal loss during the first two months of hospital stay, resulting in an 27.5% reduction from the initial weight on admission. Such a significant weight loss may be attributed to the severity and subsequent complications of the disease.

There is a rapid weight loss during the metabolic stress period (greater than 10%). Following recovery, characterized by a shift to anabolic metabolism (i.e. cessation of insulin and growth hormone resistance), protein-calorie administration is increased to replete injury-related deficiencies of body cell mass and electrolyte reserve. Increased glucose delivery stimulates insulin secretion, resulting in the increased cellular uptake of phosphate, potassium, magnesium (intracellular ions), and water, along with glucose. This electrolyte shift can lead to a rapid and profound decrease in serum phosphate concentrations in critically ill patients whose body compartment phosphate stores have already been markedly depleted during the acute metabolic stress period.

In one study on adult ICU patients, those who developed hypophosphatemia had a significantly longer mechanical ventilatory requirement and hospital length of stay when compared with patients who were not hypophosphatemic [4]. A reduction of serum phosphate levels to less than 1.5 mg/dL in adult patients can result in cardiac and respiratory failure, hypotension, and potentially fatal arrhythmias, as well as neurological compromise, including seizures and coma [1, 2, 12].

Multiple concomitant micronutrient deficiencies may also occur, the most notable being thiamin deficiency, which may impair glucose access to the Krebs cycle [2], and exacerbate already-existing energy deficiencies related to hypophosphatemia. Glucose overfeeding also lead to hyperglycemia with hepatic overload, potentially resulting in hepatic parenchymal injury (as manifested by increased serum concentrations of hepatic enzymes) followed by increased hepatocellular steatosis [3].

This entire sequence of events is extremely damaging and may be fatal to the patient, who is already compromised due to illness [13]. Clinically speaking, there is a simultaneous worsening of heart and respiratory functions, basic acid balance, hepatic and immunologic function, all calling for urgent early diagnosis and rapid intervention [2,3]. Unfortunately, the early clinical features of refeeding syndrome are relatively non-specific and can easily go unrecognized or be incorrectly attributed to other causes if not anticipated clinically.

In our patient the refeeding syndrome was suspected on the basis of decreased serum phosphate levels in concert with increased serum hepatic enzyme concentrations, which were not attributable to other etiologies. Drugs, viral hepatitis, ischemic injury as well as underlying diseases must be ruled out as causes of elevation in hepatic enzymes. Reducing caloric delivery from 2.000 to 1.520 kcal/day resulted in clinical and laboratory improvement within a week without any need for further intervention.

The ideal nutrition of an ICU child should provide the energy required, without excess or deficit, should spare protein catabolism, and should offer at least the daily recommended equivalent for micronutrients [5, 6]. Energy needs should be adjusted daily, ideally using methods such as indirect calorimetry, if available [14].

It is important to consider the risk of refeeding syndrome in children recovering from acute metabolic stress states, especially those who have had a protracted clinical course of critical illness and have undergone substantial depletion of body cell mass. In these children, enteral or parenteral nutrition should be

advanced at a reduced rate (at 20-25% of goal estimated requirements per 24-48 hour period, based on age and gender) to lessen the likelihood of developing refeeding syndrome. If indirect calorimetry is not available, only basal metabolic needs should be delivered until serum C-reactive protein falls below stress levels (< 2 mg/dL) in association with acute illness. This method permits to advance energy delivery without overfeeding infants during the acute phase of the metabolic response to injury [15].

In addition to phosphorus, there is risk of depletion of potassium and magnesium during nutritional repletion. These minerals are deposited in newly synthesized cells and serum levels may decrease in the absence of supplementation. The clinical expression of hypokalemia and hypomagnesemia overlap those of hypophosphatemia and may have a synergistic deleterious effect [1]. Although they have been reported in the literature, we did not find hypokalemia and hypomagnesemia in our patient, possibly because of the availability of these electrolytes in the body storage. As major components of the intracellular space, the body depletion may not reflect serum concentrations, as extra cellular fluid concentrations are maintained. Serum phosphate, potassium, magnesium, calcium, creatinine and blood urea nitrogen levels should be measured until goal nutritional delivery rates have been reached and low serum electrolyte levels should be repleted [16-18].

Supplementation of thiamine, riboflavin, folic acid, pyridoxine, vitamin C, as well as fat soluble vitamins is recommended [2, 10].

CONCLUSION

The refeeding syndrome represents a series of metabolic complications which take place during rapid nutrient administration in malnourished patients. Although an important cause of morbidity and a potentially fatal condition, it is still under-recognized. Clinicians ought to outlook for signs and symptoms of refeeding syndrome in the high risk patients, diagnose it early and institute appropriate measures to correct it. Children with depleted body cell mass on the basis of critical illness are at risk of refeeding syndrome. This should be taken into account when commencing nutritional support, which should be undertaken gradually and accompanied by appropriate clinical surveillance to prevent the development of dangerous electrolyte deficiencies, particularly hypophosphatemia.

CONTRIBUTORS

FISS reviewed the literature and prepared the original draft; HPL designed the study and wrote the final manuscript with significant input of WJC, who contributed to writing; WBC reviewed and approved the manuscript.

REFERENCES

[1] Solomon SM, Kirby DF. The Refeeding Syndrome: A Review. JPEN J Parenter Enter Nutr 1990; 14: 90-97. http://dx.doi.org/10.1177/014860719001400190

[2] Mehta NM, Bechard LJ, Dolan M, Ariagno K, Jiang H, Duggan C. Energy imbalance and the risk of overfeeding in critically ill children. Pediatr Crit Care Med 2011; 12: 398-405. http://dx.doi.org/10.1097/PCC.0b013e3181fe279c

[3] Dickerson RN. Refeeding Syndrome in the Intensive Care Unit. Hosp Pharm 2002; 37: 770-75.

[4] Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg 1996; 131: 1043-7. http://dx.doi.org/10.1001/archsurg.1996.01430220037007

[5] Chwals WJ. Overfeeding the critically ill children: Fact or Fantasy? New Horizons 1994; 2: 147-55.

[6] Agus MSD, Jaksic T. Nutritional support of the critically ill child. Curr Opin Pediatr 2002; 14: 470-81. http://dx.doi.org/10.1097/00008480-200208000-00020

[7] World Health Organization. Physical Status. The use and interpretation of anthropometry. WHO Technical Report Series 854, Geneva 1995; pp. 452.

[8] FAO/WHO/UNU Expert Consultation. Energy and protein requirements. WHO Technical Bulletin No 724. Geneva, Switzerland 1985.

[9] Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN 2002; 26: 126SA-128SA.

[10] Afzal NA, Addai S, Fagbemi A, *et al*. Refeeding syndrome with enteral nutrition in children: a case report, literature review and clinical guidelines. Clin Nutr 2002; 21: 515-20. http://dx.doi.org/10.1054/clnu.2002.0586

[11] Dunn RL, Stettler N, Mascarenhas MR. Refeeding Syndrome in Hospitalized Pediatric Patients. Nutr Clin Pract 2013; 18: 327-32. http://dx.doi.org/10.1177/0115426503018004327

[12] Fisher M, Swipser E, Schneider M. Hypophosphatemia secondary to oral refeeding in anorexia nervosa. Int J Eat Disord 2000; 28: 181-7. http://dx.doi.org/10.1002/1098-108X(200009)28:2<181::AID-EAT7>3.0.CO;2-K

[13] Weinsier RL, Krumdiek CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Am J Clin Nutr 1981; 34: 393-99.

[14] Muller JM, Bosy-Westphal A. Assessment of energy expenditure in children and adolescents. Curr Opin Clin Nutr Metab Care 2003; 6: 519-30. http://dx.doi.org/10.1097/00075197-200309000-00005

[15] Letton RW, Chwals WJ, Jamie A, *et al*. Early postoperative alterations in infant energy use increase the risk of overfeeding. J Pediatr Surg 1995; 30: 988-93. http://dx.doi.org/10.1016/0022-3468(95)90327-5

[16] Flesher ME, Archer KA. Leslie BD, *et al*. Assessing metabolic and clinical consequences of early enteral feeding in the malnourished patient. JPEN 2005; 29: 108-17. http://dx.doi.org/10.1177/0148607105029002108

[17] Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ 2008; 336: 1495-8. http://dx.doi.org/10.1136/bmj.a301

[18] Machado JD, Suen VM, Chueire FB, Marchini JF, Marchini JS. Refeeding syndrome, an undiagnosed and forgotten potentially fatal condition. BMJ Case Rep 2009; 2009. doi: pii: bcr07.2008.0521. 10.1136/bcr.07.2008.0521

Received on 08-10-2013 Accepted on 02-12-2013 Published on 10-03-2014

http://dx.doi.org/10.6000/1929-4247.2014.03.01.7

© 2014 de Souza *et al*.; Licensee Lifescience Global.
This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.