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Case Report

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Role of Thiamine in Refeeding Syndrome in Children

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Abstract

Purpose, Setting and Subjects: *We conducted a case report study of a postoperative pediatric patient on total parenteral nutrition managed by a multidisciplinary team in a tertiary care hospital. In October 2020, data of nutritional status, hypophosphatemia, electrolyte and metabolic imbalance, and the role of thiamine supplement were reviewed.*

Background: *Refeeding Syndrome is usually defined as the possibly lethal maldistribution of fluids and electrolytes that could take place in malnourished patients receiving enteral or parenteral refeeding. This is due to hormonal and metabolic disturbances that may lead to critical clinical deterioration. The biochemical key feature of Refeeding Syndrome is hypophosphatemia. In general, the syndrome is complicated and may also incorporate abnormal electrolytes and fluid balance; changes in serum level of protein, glucose, and the metabolism of fat; thiamine deficiency; hypokalemia; and hypomagnesaemia.*

Case Report: *an ex-preterm 6-year-old boy who underwent major intestinal resection due to necrotizing enterocolitis (NEC) during his stormy neonatal period, presented to ED with constipation for 2 days; the patient was admitted in the pediatric ward under combined care with Pediatric Surgery, as a case of large bowel obstruction for conservative management. He had cachexic appearance, global developmental delay (GDD), and faltering growth. Subsequently and during his PICU stay, he suffered a fluctuating course of electrolytes imbalance a few days after commencing total parenteral nutrition (TPN), and developed altered mental status that responded well to thiamine infusions to resume his baseline sensorium within 48 hours.*

Conclusions: *The role of thiamine in Refeeding Syndrome is extremely underestimated, despite the current evidence of its high efficacy. However, the fussy exclusion mechanism to reach the diagnosis is probably the reason behind the delaying of treatment in most of the cases. A wide range of patients are at risk of developing Refeeding Syndrome, especially malnourished children, as in this case report.*

Categories: *Nutrition, Surgery, Pediatrics, Gastroenterology.*

Keywords: Short Bowel Syndrome, Thiamine Deficiency, Refeeding Syndrome, Wernicke Encephalopathy

Patient: Male, 6-year-old
Final Diagnosis: Refeeding Syndrome.
Symptoms: Disorientation, Inactiveness.
Medication: Thiamine 100mg injection.
Clinical Procedure: Adhesiolysis, Intestinal Resection, Anastomosis, and Stoma.
Specialty: Pediatrics, Surgery.
Objective: Unknown etiology.

Introduction

The Refeeding Syndrome

Refeeding Syndrome is usually defined as the possibly lethal maldistribution of fluids and electrolytes that could take place in malnourished patients receiving enteral or parenteral refeeding. This maldistribution is due to hormonal and metabolic disturbances that may lead to critical clinical deterioration. The biochemical key feature of Refeeding Syndrome is hypophosphatemia. In general,

the syndrome is complicated and may also incorporate abnormal electrolytes and fluid balance; changes in serum level of protein, glucose, and the metabolism of fat; thiamine deficiency; hypokalemia; and hypomagnesaemia [1]. In other words, over the past 60 years, Refeeding Syndrome (RS) has been known for the resultant biochemical disturbance, signs, and symptoms of the deleterious effects of feeding after a period of prolonged starvation [2].

Incidence Rate

The exact occurrence rate of Refeeding Syndrome is unknown — to some extent attributed to the lack of a consensus universal definition. In a conducted research of 10,197 admitted patients, the severe hypophosphatemia incidence was 0.43%, reporting malnutrition as one of the top risk factors [1]. Additionally, in the UK, the experts of a large study into parenteral nutrition (PN) care, found Refeeding Syndrome to have occurred in 4% of cases of parenteral nutrition, after using wide diagnostic criteria [2].

In a multicenter retrospective cohort study that performed on patients under 3 years old, who were admitted with a primary diagnosis of faltering growth and otherwise healthy children, none of the 179 children meeting inclusion criteria had laboratory evidence of Refeeding Syndrome [3].

Moreover, in a determining retrospective cohort study conducted in the Medical University of South Carolina Children's Hospital, about the incidence of Refeeding Syndrome in the first week postnatally, defined by hypophosphatemia in very-low-birthweight (VLBW) infants with intrauterine growth restriction (IUGR) comparing them with those without IUGR, IUGR infants were remarkably more likely to have hypophosphatemia (41% vs. 8.9%), relative risk (95% confidence interval), and severe hypophosphatemia (11.4% vs. 1%) [4].

Taking the other extremity of age (adults) as a field for study of the incidence of Refeeding Syndrome, a Dutch study in the Department of Internal Medicine with 178 participants included in the study, 97 (54%) were taken to be at risk of developing Refeeding Syndrome and 14 patients in fact developed the syndrome (14% of patients at risk and 8% of study population). Individuals with a malignancy or previous malignancy were at heightened risk of developing Refeeding Syndrome [5].

Thiamine

Vitamin B1, or thiamine, is a water-soluble vitamin that was first described in the 1920s; it was one of the first components to be described as a vitamin. It contributes to plentiful functions in the body, including nervous system (axonal conduction) and muscular functionality (flowing of the electrolyte in the cells), metabolism of carbohydrate, processing of enzymes, and producing the digestion requirement of hydrochloric acid [6].

Thiamine is a substantial water-soluble vitamin crucial for amino acid and carbohydrate catabolism and gluconeogenesis. To be precise, Thiamin Pyrophosphate (TPP) is considered for 2 enzymes a cofactor in oxidative pathways after glycolysis: the complex of pyruvate dehydrogenase, utilized to convert pyruvate to Acetyl-CoA, and the complex of α-ketoglutarate dehydrogenase, used to convert α-ketoglutarate to succinyl-CoA [7].

A significant cause of acute or subacute delirium, Wernicke encephalopathy (WE) is a neurological defect resulting from thiamine – vitamin B1 – deficiency. WE is the most critical encephalopathy due to one vitamin deficiency. WE is diagnosed clinically with the classic triad of ocular findings (ophthalmoparesis), cerebellar dysfunction (ataxia), and confusion. The syndrome of Korsakoff amnesia is a late neuropsychiatric manifestation of WE with confabulation – which is making up stories to fill in any gaps in memory – and memory loss; sometimes, the condition is referred to as Wernicke-Korsakoff psychosis or Wernicke-Korsakoff syndrome (WKS). Chronic alcoholism is characteristically associated with thiamine deficiency because thiamine uptake and utilization is affected by alcohol. However, WE may develop in nonalcoholic conditions, such as prolonged starvation, bariatric surgery, and can even occur in healthy infants fed thiamine-deficient formulas [8].

Thiamine's concentration is extremely low in the intestinal lumen, while it is in a free form. Absorption occurs primarily in the proximal part of the small intestine by means of two mechanisms, which is diffusive at high concentrations, and saturable at lower (physiological) [9].

Pediatric Short Bowel Syndrome

A suggested definition for short bowel syndrome (SBS) in children is the need for intravenous nutritional and fluid supplementation in those below 25% of remaining small bowel that is anticipated for gestational age. This syndrome results from the alteration of intestinal absorption and digestion that takes place after extended resection of bowel. It is a complicated disorder with metabolic, nutritional, and infectious consequences. Obstruction of bowel is a potential complication of SBS [10]. The length of the small intestine in neonates is about 250 cm. By adulthood, it grows to approximately 750 cm. As an outcome, the infants and young children have a positive long-term prognosis compared to adults regarding potential intestinal growth following intestinal resection. The adaptation of the intestine may take months to be reached; in the meantime, children who have had resection of the intestine need nutritional support through varied therapeutic actions, including parenteral nutrition. The duodenum and jejunum are responsible for the absorption of most dietary constituents except vitamin B12 and bile acids. However, the small intestinal sites of nutrient absorption are as follows, starting from its end: distally the ileum-bile acids, and vitamin B12; midway the jejunum-carbohydrates, proteins, fat, vitamins; and initially the duodenum-iron [11].

Case Report

A 6-year-old boy who underwent major intestinal resection due to necrotizing enterocolitis (NEC) during his stormy neonatal period,

presented to ED with constipation for 2 days (very unusual for *him as he used to pass around 6 motions per day) with vomiting once, poor intake and occasional abdominal pain. No fever, and systemic inquiry was unremarkable. His extreme previous prematurity resulted in a group of sequelae in the form of mild Cerebral Palsy (CP), Short Bowel Syndrome (SBS) post NEC surgery and Faltering Growth, then lately diagnosed with Overflow Constipation (thought to be actual diarrhea due to SBS) leading to Chronic Intestinal Obstruction, and significant Small and Large Bowel Dysfunction.

He used to be on milk formula and soft diet with poor feeding habits and weight gain, otherwise, no known allergies or other chronic illnesses. On initial examination he looked unwell, cachexic, afebrile, dehydrated, not in pain, and his abdomen was mildly distended, not tender, soft, and lax despite X-ray and US findings. Benign systematic examination and initial vitals except for tachycardia.

The patient was admitted to pediatric ward under combined care of pediatrics and pediatric surgery departments, as a case of large bowel obstruction for conservative management. Upon admission, basic investigations confirmed large bowel obstruction with a suspicion of left bowel mass. He was kept NPO, started on IV fluids and IV Paracetamol, nasogastric tube inserted and put on free drain along with ceftriaxone and metronidazole to cover for the possibility of bacterial overgrowth in a known short bowel. Afterwards, ordered abdominal CT-scan showed an intramural mass at the level of splenic flexure with intestinal obstruction. The pediatric surgeon preferred a direct visualization of the mass and possible biopsy before rushing to laparotomy – as the patient wasn't significantly symptomatic. On the next day, a colonoscopy was done and revealed the presence of fecal impaction with no possibility to be managed endoscopically. This was followed by exploration laparotomy, adhesiolysis (a surgical procedure that removes bowel adhesions), resection of chronically necrotic bowel, creating an ileostomy and colostomy. Postoperatively, he was shifted to PICU, the above-mentioned medications continued in addition to IV omeprazole and morphine, antibiotics adjusted to piperacillin-tazobactam and metronidazole and put on nasal cannula oxygen.

The following day, he deteriorated into septic shock. He was electively intubated, ventilated, sedated and antibiotics were again switched to meropenem and vancomycin.

Over the following days, he progressed to multi-organ failure in the form of acute kidney injury, disseminated intravascular coagulation (DIC) and transaminitis, respiratory and circulatory decompensations. During this period of critical illness, nutrition was certainly important; hence, TPN with intra-lipid started on day 2 postoperatively. These flaws responded well to supportive treatment (during which, TPN and intra-lipid were still received). A couple of days after general condition improvement post-extubation, he was noticeably less interested in the surroundings and less interactive with his parents. Blood indices showed low serum potassium and phosphorus, raising the suspicion of Refeeding Syndrome. He was started on Thiamine IV 100 mg daily and high dose multivitamins via NGT for 3 days (improvement was noticed on day 2 of treatment without major changes to the caloric intake).

Over the subsequent few days and throughout whole PICU admission, he was kept NPO, labs done on daily basis including U/E to adjust the TPN while having acute kidney injury, then monitoring for TPN side effects.

Before planning enteral feeding, a barium meal and follow through were done to show marked dilatation of the small bowel with no evidence of obstruction, associated gastroesophageal reflux disease and delayed gastrointestinal motility, which was evidenced by a following abdominal X-ray, which showed filling contrast, and marked dilatation of the small bowel. However, there was no evidence of air fluid levels and no abnormal radiopaque shadows as well. The Pediatric Gastroenterologist recommended domperidone as prokinetic, alternate Augmentin and Metronidazole via NGT to manage possible bacterial overgrowth, 10-20ml of ileostomy output flushed every other day into the colostomy to avoid diversion colitis. In spite of NGT drain becoming less, he did not tolerate even small continuous feeds using Peptamen Junior formula. Upper GI scope showed almost absent villi and a poor small bowel condition with gross dilatation (his parents were educated and counselled about the possibility of long term TPN).

A second feeding trial resumed using Neocate milk formula. The child was transferred to a pediatric ward after resolution of all critical comorbidities; he continued on antibiotics, PPI, domperidone, TPN with intra-lipids while monitoring electrolytes. Other labs done as needed and physiotherapy started.

In less than one week after this, he developed features of nosocomial pneumonia, worsened rapidly, and passed away after developing acute respiratory distress syndrome and pulmonary hemorrhage.

Discussion

Given the fact that our patient had multiple risk factors and the sequence of events – alternation of mental status and hypophosphatemia in day 5 of parenteral nutrition – led to him developing Refeeding Syndrome (RS), the diagnosis was made. However, it was after excluding other feasible and more common causes of his presentation. Although Wernicke encephalopathy (WE) – the neurological emergency with the characteristic triad generated by a deficiency of thiamine – has alcohol abuse as its most common underlying etiology, a gastrointestinal surgery, or prolonged starvation, can also lead to WE counting on the fact that our patient didn't fulfill the WE criteria, the diagnosis was ruled out [12]. However, Wernicke-Korsakoff Psychosis or Wernicke-Korsakoff Syndrome (WKS) was not applicable to be considered. Furthermore, it is worth mentioning that their signs and symptoms are not always linked to RS as we encountered in this case.

Nevertheless, our patient's end could be attributed as a late complication of the long-term thiamine deficiency, topping up his bad nutritional status over his poor dietary absorption by his partially resected GI tract. In a study conducted in 2003 of several hundred infants, about the short and long-term outcomes of thiamine-deficient formula-fed children who were not immediately diagnosed, it was confirmed that a group of patients – around thirty six percent – passed away due to cardiopulmonary complications, and the surviving children had intellectual disabilities, a delay in their neurodevelopment, and significant motor dysfunction by 9 years old [13].

Interesting, as in a long-term follow-up, SBS correlation with thiamine deficiency was found only in 10% of the cases in an Argentinian study [14].

However, this case demonstrates how far unrecognized/untreated constipation can affect intestinal viability and functionality, and eventually the child's growth and development. Overflow diarrhea was a major cause that his constipation was missed over the years, while assuming that his short bowel was the reason of occasional loose stools on a daily basis. This requires raising awareness about such a detrimental symptom.

Conclusion

The role of thiamine in Refeeding Syndrome is extremely underestimated, despite the current evidence of its high efficacy. However, the fussy exclusion mechanism to reach the diagnosis is probably the reason behind the delaying of treatment in most of the cases. A wide range of patients are at risk of developing Refeeding Syndrome, especially malnourished children, as in this case. More extensive studies of the effect of thiamine in children during RS are needed.

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Disclosure

Human Subjects: Written consent was obtained from all participants in this study.

Conflicts of Interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

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