

## Case Report

# Thiamin and folic acid deficiency accompanied by resistant electrolyte imbalance in the re-feeding syndrome in an elderly patient

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**Introduction:** Re-feeding Syndrome (RS) is a deadly complication, which can be encountered during “re-feeding” of malnourished patients. In these patients, thiamin deficiency may develop and “risk awareness” is the most significant factor in the management of these patients. In this case report, the treatment is presented of an elderly patient who was diagnosed with RS and followed-up in the intensive care unit (ICU) due to resistant fluid-electrolyte imbalance. **Case:** An 87-year-old elderly woman was admitted to the hospital due to aspiration pneumonia. On day 4, during parenteral nutrition (30 kcal/kg/day), severe electrolyte imbalance developed. Total parenteral nutrition (TPN) was stopped, and enteral feeding together with potassium (90 mmol/day, i.v.) were started. During follow-up, plasma potassium values remained less than 3 mmol/L. Despite replacement therapy, hypoalbuminemia, hypomagnesemia, hypocalcemia, and hypophosphatemia persisted. Considering the parenteral nutrition (30 kcal/kg/day) during the hospitalization period, a diagnosis of RS was made. On day 10, thiamin (200 mg/day, i.v.) and folic acid (5 mg/day) were added, and the patient subsequently responded to electrolyte replacement treatment. The patient was discharged on day26 with a home-care plan. **Conclusion:** In patients with malnutrition, thiamin replacement should be given before starting nutrition to prevent RS. Energy intake should be 10kcal/kg/day at the start, and be gradually increased between days 4-10. Hemodynamic-laboratory parameters should be closely monitored. All these measures may be life-saving for patients at high risk.

**Key Words:** malnutrition, thiamin, folic acid, electrolyte imbalance, re-feeding syndrome

## INTRODUCTION

Malnutrition is defined as insufficient nutrition or nutritional disorder due to diseases, and is frequently seen in the elderly. Interest in diagnosis and treatment of patients with malnutrition is increasing in parallel with the increasing geriatric population.<sup>1</sup>

Re-feeding Syndrome (RS) is a deadly complication, which can be encountered during “re-feeding” of malnourished patients.<sup>2</sup> Prolongation of insufficient nutrition for more than 5 days and BMI <16 kg/m<sup>2</sup> are the most important factors for the development of RS. The other significant risk factors are more than 15% weight loss in 3 to 6 months and decreased serum electrolyte-vitamin levels before nutrition treatment. This syndrome generally starts with mild symptoms due to a relative insufficiency of thiamin, phosphate, potassium and magnesium under the influence of the insulinergic system activated by carbohydrate intake, and it may lead to cardiac and neurological conditions with increasing severity over time.<sup>3</sup>

The metabolic balance may be easily disturbed by accompanying comorbidities in malnourished advanced age

patients, and management of this process may be highly challenging. In RS, “risk awareness” is the most important step, but the inclusion of a detailed clinical evaluation, multidisciplinary approach and nutrition plan should not be disregarded.

In this paper, the treatment is presented of an elderly patient who was diagnosed with RS and followed-up in the intensive care unit (ICU) due to resistant fluid-electrolyte imbalance.

## CASE

An 87-year-old elderly woman with advanced Alz-

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heimer's disease was admitted to the hospital due to poor general condition and aspiration pneumonia. Since hypernatremia was detected on admission to the emergency room, a 5% glucose infusion was ordered by the emergency physician for volume replacement. On day 2 after admission, parenteral antibiotic treatment and total parenteral nutrition (TPN) (30 kcal/kg/day) were initiated as an alternative to oral nutrition. On day 4, the general condition deteriorated and severe electrolyte imbalance developed as a refractory low potassium level in the plasma. We were informed of this management strategy when a consultation was requested from our department, and this strategy was considered unsuitable. The patient was cachectic without renal or gastrointestinal system pathology - 45 kg, body mass index (BMI): 16, abdominal circumference: 70 cm, arm circumference: 21.5 cm, triceps skinfold thickness: 6 mm, abdomen skinfold thickness: 6 mm, and was not using any agents which could lead to potassium loss. TPN was discontinued and enteral nutrition and i.v. potassium (90 mmol/day), magnesium (0.5 mmol/day) and 10% human albumin (100 mL/day) were initiated. During follow-up, serum potassium was under 3 mmol/L and it was learned that for the previous 2 months, the patient had not been taking the methimazole treatment prescribed for nodular goiter. TSH was 0.0027 IU/ml and FT4 was 20.6 pmol/L. Methimazole 5 mg 1x1 was started via nasogastric tube. The pneumonia of the patient improved but the need for i.v. electrolytes continued and the clinical condition deteriorated. During the same period of time, there was a worsening of edema (3+) in the legs. The chest x-ray showed cardiothoracic proportion within normal limits and the electrocardiography (ECG) demonstrated a regular rhythm. RS was diagnosed due to low BMI, presence of hypoalbuminemia, hypomagnesaemia, hypocalcemia and hypophosphatemia in spite of replacement (Table 1) and administration of TPN 30 kcal/kg/day. Nutritional support was reduced to 10 kcal/kg/day by the enteral route. On day 10 of hospitalization, thiamin i.v. 100 mg/day and folic acid 5 mg/day were added to the treatment. The patient's minimum phosphate concentration was 0.61 mmol/L. Enteral and parenteral phosphate

preparations were not available. During follow-up, the patient's phosphate concentration increased to 1.32 mmol/L (0.90-1.3 mmol/L). There was no need for magnesium replacement. After thiamin and folic acid supplementation, the patient responded to the electrolyte replacement treatment, and was discharged on day 26.

## DISCUSSION

With increased interest in the diagnosis and treatment of elderly patients with malnutrition, an awareness of RS has become more important.<sup>4</sup> RS, which may often be overlooked, is a clinically significant syndrome including electrolyte imbalance, fluid retention and dysfunction of various organs, which may be seen in patients receiving enteral or parenteral nutrition following prolonged fasting.

When nutrition is started following a prolonged starvation period or malnutrition, complications are seen in the first week if appropriate measures are not taken. The identification of patients at high risk of RS and close monitoring with a well-planned nutritional programme are very important. The prolongation of insufficient nutrition for more than 5 days and BMI <16 kg/m<sup>2</sup> are the most important factors in the development of RS. Other significant risk factors are weight loss of more than 15% in 3 to 6 months and decreased serum potassium, phosphate and magnesium levels before nutrition treatment.

Fluid and electrolyte imbalance may be observed following the initiation of nutritional support and may occur as hypopotassemia, hypomagnesaemia and hypocalcemia. Therefore, in cases of significant deficiency in serum electrolytes, electrolyte replacement must be applied first and before starting nutrition.<sup>5</sup>

During prolonged fasting, insulin secretion is reduced secondary to reduced carbohydrate intake. In this case, energy is provided in general by lipolysis instead of glycogenolysis, and proteins are relatively preserved. Consequently, intracellular phosphate, potassium and magnesium may be depleted, even when the serum level is normal.<sup>6</sup> In the case of re-feeding with a high glucose-based nutritional regimen, there will be a shift from fat towards carbohydrate in the metabolism with the secretion of in-

**Table 1.** Blood test result of the patient

	Day 1	Day 2	Day 5	Day 7	Day 9	Day 12	Day 16	Day 22	Day 26	Normal range
Glucose (mg/dl)	141	-	118	119	101	152	126	119	128	70-105
BUN (mg/dl)	64	42	30	21	14	23	27	27	38	21-43
Creatinine(mg/dl)	0.8	0.6	0.36	0.33	0.36	0.45	0.36	0.43	0.43	0.4-1.2
AST (U/L)	11	8	9	9	13	13	10	17	24	5-34
ALT (U/L)	<6	7	<6	<6	9	13	10	13	27	0-55
Total protein (g/dL)	6.1	-	5.9	-	-	5.2	-	5.1	5.6	6.2-8
Albumin (g/dL)	2.9	2.5	2.4	2.4	2.4	2.6	3	3.1	3.1	3.5-5
K (mmol/L)	3.7	3.0	2.7	2.6	2.7	3.7	3.1	5	4.5	3.5-5.1
Ca (mg/dL)	8.5	8.1	7.8	6.7	7.3	7.9	8.6	8.7	8.7	8.4-10.2
Phosphate (mmol/L)	-	0.8	0.8	0.8	0.6	0.8	1	1.2	1.3	0.9-1.3
Na (mEq/L)	147	140	133	130	126	130	135	138	137	136-145
Chloride (nmol/L)	-	-	99	-	94	-	101	-	-	96-105
Mg (mg/dl)	-	1.47	1.57	1.47	1.88	1.36	1.35	1.58	1.84	1.6-2.6
Folate (ng/mL)	1									3-20
B-12 (pg/mL)	312									137-883

BUN: blood urea nitrogen; AST: alanine aminotransferase; ALT: aspartate aminotransferase; K: Potassium; Ca: Calcium; Na: Sodium; Mg: Magnesium.

sulin into the circulation, and the substrates which are necessary for glucose metabolism are quickly consumed. These substrates are phosphate and magnesium, which provide the formation of intracellular adenosine triphosphate and glucose attracted to the intracellular area with potassium and thiamin. Although there is an increased requirement, a significant drop is seen in serum phosphate, potassium and magnesium levels. When glucose support continues, endogenous insulin secretion is stimulated. Increased insulin can exacerbate hypopotassemia, hypomagnesaemia and hypocalcemia, causing potentially lethal neurological and cardiovascular complications.<sup>7</sup>

Mild, moderate or severe hypophosphatemia can be seen in cases of re-feeding. Mild hypophosphatemia (<0.6 mmol/L) is asymptomatic and rapidly reversed. A moderate degree of hypophosphatemia (0.3-0.6 mmol/L) may be overlooked, as when these patients are admitted to hospital, the serum phosphate concentration is generally within the reference range. At times, the ensuing hypophosphatemia can be profound. Depending on the severity of the hypophosphatemia (<0.3 mmol/L), the patient may complain of muscle weakness or may develop the full-blown hypophosphatemic syndrome. In this particular clinical situation, if the practitioner does not have a high index of suspicion, the delirious state can be misinterpreted as delirium tremens. Moreover, as has been seen in cases of thiamin deficiency with dementia (such as in advanced stage Alzheimer's disease), the neurological signs of hypophosphatemia may be masked.<sup>8</sup>

The lowest phosphate concentration in the current patient was 0.61 mmol/L. No enteral or parenteral phosphate preparations were available, and the phosphate concentration increased to 1.32 mmol/L (0.90-1.30 mmol/L) in the subsequent clinical course, obviating the need for replacement.

During dextrose infusions, the deposition of glycogen in the liver reduces the potassium level in the blood. For 1g of glycogen to be deposited, 0.36mmol potassium is required. Potassium is an important regulator of glycogen synthesis in the muscle cells, and in the presence of hypopotassemia, a sufficient amount of glycogen may not be produced.<sup>9</sup>

Thiamin deficiency is especially important in RS. Thiamin is an important co-factor required for enzymatic reactions in carbohydrate metabolism. Increased metabolic activity and thiamin requirement due to carbohydrate usage may lead to "relative" thiamin deficiency. Symptoms are in general non-specific, including headache, weakness, confusion, ophthalmoplegia, ataxia, abdominal discomfort, and cardiovascular conditions similar to heart failure in more serious cases. These patients may be frequently overlooked at diagnosis. Thiamin supplementation should be initiated before the institution of nutrition in advanced age patients with severe malnutrition. In healthy adults, the thiamin requirement is 0.5 mg for 1000 kcal.<sup>10,11</sup>

Although the European Federation of Neurological Societies (EFNS) and the Royal College of Physicians recommend very high dosages (IV 3x200 mg or 1x500 mg), there is no consensus on the optimal dosage of thiamin. Hershkowitz et al<sup>12</sup> reported that thiamin i.v. 100 mg for 2

days in patients with thiamin deficiency provided a significant improvement in the clinical condition.

The current patient was at an advanced stage of Alzheimer's disease, so consciousness could not be precisely evaluated. However, there was no acute neurological sign during follow-up visits. The patient responded well to pneumonia treatment but severe edema developed without acute heart failure. The patient was diagnosed with RS and thiamin and folate were supplemented. Dramatic improvements were seen in electrolyte values, thereby justifying the diagnosis of RS.

In this group of patients, intestinal folate absorption is impaired as a result of inadequate nutrition due to neurological diseases, reduced liver function and changes in the metabolism and therefore folate levels may be affected.<sup>13</sup> Sheridan et al<sup>14</sup> indicated that detection of folate and thiamin deficiency was a predictor risk for severe malnutrition and RS. In addition, they stated that cases with profound anemia due to nutritional deficiency were at higher risk of RS development and that these patients should be closely monitored in this regard.

In malnourished patients at risk of RS, nutritional supplements should be administered incrementally to provide sufficient vitamin and mineral supplementation. Close monitoring is also required for vital signs, electrolytes, peripheral edema and changes in the mental status. In general, the recommended nutritional regimen is to start with 10-15 kcal/kg daily for the first 3 days, then to increase to 20 kcal/kg on days 4 to 6 and finally to increase to 20-30 kcal/kg on days 7 to 10 if there is no sign of re-feeding.<sup>15,16</sup>

The enteral nutrition of the current patient deteriorated due to highly advanced Alzheimer's disease and she was admitted to hospital with BMI 16. During the first days, dextrose-containing fluids and nutritional support of 30kcal/kg resulted in RS. Thiamin and folate were added to the treatment on Day 10, the clinical condition improved and electrolytes reached normal limits.

### Conclusion

In advanced aged and malnourished patients under polypharmacy due to comorbidities, who are at risk of RS, the administration of thiamin replacement and initiating energy intake as 10 kcal/kg/day, increasing in 4 to 10 days with close follow-up of hemodynamic parameters, may be lifesaving.

Written informed consent was obtained from a family member of the patient.

### AUTHOR DISCLOSURES

No conflict of interest was declared by the authors

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