

REFEEDING SYNDROME IN SCHIZOPHRENIA CASE REPORT

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Abstract

Introduction: Recent studies have shown growing concern for refeeding syndrome (RFS) among patients suffering from other medical conditions, although the exact incidence in this population is unknown. The phenomenon is also present among patients with mental health conditions characterised by poor feeding, poor appetite, catatonic features, and poor cognitive functioning. Generally, RFS occurs with the reintroduction of calories to severely malnourished patients. It becomes critical for clinicians to have a high incidence of suspicion for prompt diagnosis and appropriate management to keep them alive if the malnutrition does not take their lives.

Case Presentation: We report a case of a 53-year-old man with an 8-year history of schizophrenia and a 3-month history of poor feeding. We admitted him because he refused to feed or drink for two weeks. As a result, he

was severely malnourished, and we started refeeding while dealing with his psychotic symptoms. He gained about 2kg within a week of admission, but that was fraught with metabolic derangements, which included hypophosphatemia, hypomagnesaemia, and hypocalcaemia. We revised his diagnosis to RFS in schizophrenia and managed it as such.

Conclusion: There are no agreed biomarkers for the diagnosis of Refeeding Syndrome, and the diagnosis is mainly clinical, supported by electrolyte deficiencies. Unfortunately, hypophosphatemia does not have readily available formulations for its correction, which can lead to neurological, cardiovascular, and other complications, including sudden death. Delay in diagnosis worsens the prognosis, and the intuitive desire to feed a starved patient zealously leads them to death.

Key words: Case report, hypophosphatemia, malnutrition, refeeding syndrome, schizophrenia

Introduction

Metabolic processes resulting in death after the introduction of feed to severely malnourished people has been known for over 70 years and was first documented in the late 40s when studies were conducted among Japanese prisoners of war.¹ It was not until 1981 that the name “*Refeeding Syndrome*” was coined by Weinsier and Krumdieck who observed the sudden death of two severely malnourished individuals who were fed over-zealously.² Despite the relatively long history, there is still no consensus on the definition and its management because of the lack of high quality scientific evidence.^{3,4} It is potentially fatal when missed, yet there are no agreed biomarkers for diagnosis. When diagnosed, treatment can be tasking, as formulations for treatment are not readily available, especially in low- and middle-income countries. Refeeding syndrome is described as “a range of metabolic and electrolyte alterations

occurring as a result of the reintroduction and/or increased provision of calories after a period of decreased or absent caloric intake”.⁴ The syndrome can happen regardless of the route (oral, enteral or parenteral) of calorie intake.

Case

A 53-year-old head pastor of a church in the capital city of the country, who is living with his wife and three children in Accra presented with a 3-month history of poor feeding, two weeks of refusing to eat anything at all, and 3 days of no water intake. He was diagnosed and managed as schizophrenia 8 years prior. He initially improved on medication but discontinued treatment after 4 years when his symptoms resolved. He was symptom-free for another 3 years and was apparently well until a year before presentation when he began to experience symptoms that included poor personal hygiene, self-neglect and social withdrawal. It was difficult to get him help as he was a highly opinionated person. During this period, only two of his assisting pastors were permitted to visit. Two weeks prior to presentation he forbade one of the pastors from visiting. On examination, he was severely malnourished and cachectic. He weighed 35kg with an estimated BMI of 12.5 kg/m². An offensive body odour was noted as a

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Conflict of Interest: None Declared

result of poor oral and personal hygiene. He had overgrown nails (about 6cm each) and could not sit up in a wheelchair unsupported. He was negativistic, had persecutory delusions and resisted treatment. He was admitted to the psychiatry department of a teaching hospital and managed by a multidisciplinary team consisting of internists, dieticians, cardiologist and a neuropsychiatrist. His laboratory findings and weights during admission is as in **Table 1**.

Table 1

Admission DAY	1	8	15	22	30
Hb (g/dL)	8.2	4.2			
Na (mmol/l)	145	164	140	136	130
K (mmol/l)	4.5	3.1	2.4	4.6	4.0
Cl (mmol/l)	109	140	112	103	98
Urea (mmol/l)	42.8	15	9	3.2	4.1
Creat (μmol /l)	263	87	105	57	47
eGFR (mls/min/1.73m ²)	27	87	70	89	>89
Calcium (2.15-2.50)		1.88	1.58	1.78	1.77
Adjusted Calcium (2.15-2.65)		2.28	2.08	2.26	2.25
Phosphate (0.81-1.45)		0.36	0.30	0.84	1.17
Magnesium (0.66-1.07)		0.78	0.56	0.84	0.64
Albumin (35-50) g/L		20	15	16	16
Weight (kg)	35	46	42	41	

He was started parenteral feeding for the first 48 hours with thiamine supplementation. Four Sub-convulsive Electrical Brain Stimulation sessions on alternate days were initiated on day 2 of admission as patient was uncooperative with nasogastric (N/G) tube. After a week he became somehow cooperative and the N/G tube was passed to deliver a high protein (1.2 g/kg) and a total of 1800 cal/day and medication via the N/G tube. Elastic stockings and subcutaneous enoxaparin prophylaxis were also added to his treatment against hyper-coagulable states. RFS was diagnosed on day 8 of admission following the gross deficits in electrolytes as indicated in the table 1. Parenteral potassium, magnesium and calcium were initiated. Phosphate was

to be replaced from his diet as there were no specific formulations available. Calorie intake was then restricted to 1000 cal/day and increased gradually to 1600 cal/day over two weeks. We observed worsening of symptoms on days that followed the days he was described as “*fed well*”.

Patient developed a bilateral pneumonia on day 10 (diagnosed by x-ray) and this could be due to a nosocomial infection coupled with his expected low immunity from the severe malnutrition. He was managed on parenteral ceftriaxone and co-amoxiclav with oral azithromycin. He improved as he was able to maintain good oxygen saturation (SpO₂). He however, developed right pleural effusion which yielded serous fluid on tapping on day 15. Nasopharyngeal swap was taken to rule out Covid-19; concurrently oral doxycycline, vitamin C and zinc were added to the treatment. On Day 34 when he developed a high-grade fever and atelectasis with bronchopulmonary fistula. He was managed with chest tube under water seal and intranasal oxygen. He died suddenly 2 days later.

Discussion

Britain’s National Institute for Health and Care Excellence (NICE) has developed a screening, assessment and management guidelines to prevent RFS or mortality if it occurs.⁵ Short Nutritional Assessment Questionnaire (SNAQ) has also been validated for screening and diagnosing malnutrition.⁶ However, both NICE and SNAQ have low sensitivity and specificity scores on retrospective validation analyses.⁴ The important thing is for clinicians to have a high index of suspicion, especially for persons who may be at risk of developing RFS such as persons with poorly managed mental health disorders, substance use disorders, malabsorption, malignancies, starvation in protests, military recruits, athletes, child abuse and critically ill patients.⁷

Despite the recognition of starvation and RFS for many years, the metabolism of starvation and the changes that occur during refeeding is not completely understood.⁸ Glucose is the main source of energy production and the excess is stored as glycogen in the liver or muscles. When glycogen store capacity is exceeded, glucose is converted to fat and stored as fatty acids in adipose tissue. This results in reduction of blood glucose levels and a consequent reduction in insulin production from the pancreatic islet cells.⁹

With starvation, the body begins to break down stored glycogen and it is depleted in about 72 hours without food. Gluconeogenesis begins from non-carbohydrate sources for obligate glucose users like

brain and erythrocytes. This is accompanied by fatty acids metabolism to form ketone bodies for production of energy. The net result of starvation is the depletion of fats, proteins, potassium, phosphate and magnesium.^{8,10} This depletion affects major organs like lung, heart, liver, intestines and kidneys with complications such as hypotension, bradycardia and hypothermia.^{11,12}

The primary goal in caring for nutritionally depleted patients is the preservation of functional protein.⁸ With the resumption of feeding, particularly glucose, there is an increased production of insulin. Insulin intrinsically enhances protein formation and prevents degradation of protein.¹³ It pushes potassium and phosphate intracellularly for phosphorylation during the breakdown of glucose in glycolysis, Krebs cycle and the electron transfer system. Hypophosphatemia is generally accepted as the hallmark of RFS even though it is not the only cause of hypophosphatemia. Other causes of hypophosphatemia include chronic alcoholism, insulin administration, vitamin D deficiency, hyperparathyroidism and Fanconi syndrome.¹⁴

Hypophosphatemia decreases Adenosine triphosphate (ATP, the *energy currency*), cyclic adenosine monophosphate (cAMP, 2nd messenger for many biological processes) and 2,3-Diphosphoglycerate (2,3-DPG, in the erythrocyte), due to decreased glycolysis.¹⁵ The 2,3-DPG fall increases haemoglobin oxygen affinity, so low phosphorus level induces tissue hypoxia. ATP levels may also decrease in myocardial and skeletal muscles and can result in dysfunction and death of various cell types and therefore the appearance of cardiovascular and neuromuscular symptoms.¹⁶

In addition to hypophosphataemia, RFS is characterised by hypomagnesaemia, hypokalaemia, thiamine and other vitamins (B₆ and B₁₂) deficiencies, trace metal deficiencies (e.g., selenium and zinc), glucose and lipid imbalance, and a spurious hyponatremia with fluid balance abnormalities. Hypomagnesaemia is associated with refractory hypokalaemia and hypocalcaemia which can lead to clinical signs and symptoms and could mask RFS symptoms.¹⁷ Thiamine is required for metabolism of pyruvic and lactic acids, and links glycolysis to the Krebs cycle. Deficiency of thiamine causes fatal acidosis.^{4,11,17} Insulin is antinatriuretic and fluid retention occurs as a sequela causing death by pulmonary oedema.¹⁹ These abnormalities to a greater extent explains the clinical features of RFS manifested by our patient. Table 2 depicts general clinical presentation.³

Table 2

	Neurological	Cardiovascular	Others
Hypophosphatemia	Weakness, paraesthesias, lethargy, confusion, coma, sudden death	arrhythmias, cardiac failure, left ventricular dysfunction,	Dyspnoea, haemolysis, increased susceptibility to infection, tissue hypoxia, rhabdomyolysis
Hypomagnesaemia	Hyporeflexia, fasciculations, psychosis, delirium, vertigo, apathy, depression, irritability	arrhythmias, ECG changes	Hypocalcaemia (tetany, ataxia, muscle weakness, tremor)
Hypokalaemia		Arrhythmias, ECG changes	Constipation, fatigue, paralytic ileus, rhabdomyolysis
Sodium retention		Fluid overload, congestive heart failure, tachycardia, peripheral oedema	Acute lung oedema, decreased haematocrit, decreased serum albumin levels
Thiamine deficiency	Dry beriberi, Wernicke's encephalopathy (nystagmus, ataxia, ophthalmoplegia, confusion), Korsakoff syndrome (anterograde and retrograde amnesia, confabulations)	Wet beriberi	

The incidence of RFS is not exactly known due to the lack of consensus of its definition and decreased awareness so being under-diagnosed. A study of inpatients of an internal medicine department revealed an incidence of 8% in the study population.²⁰ Screening patients who may be at risk of RFS and adopting the management guidelines can prevent the condition. Early diagnosis of the syndrome when it occurs with timely correction of the deficient ions and vitamins can reduce the risk of mortality.

The principle for managing RFS as agreed by the ASPEN consensus in 2019 is to "start low and go slow".⁴ The complex metabolic changes occur largely due to the fast re-introduction of calories. One can begin with 25% of the required calorie per day and graduated over the subsequent 3 - 5 days.⁴ The ions implicated

need to be monitored daily and replaced when low except for hyponatremia whose correction can cause pontine myelinosis.^{21,22} With the poor integrity of the GI tract, parenteral replacement of the ions and the vitamins may be ideal while correcting the energy deficiency.¹¹

Conclusion

The nature of many mental illnesses and other wasting chronic diseases lend itself to poor self-care and a resultant malnutrition. A high index of suspicion and screening for RFS is important for the holistic care of patients who present with chronic conditions. Reintroducing calories after starvation with zeal may be intuitive but potentially fatal. Caution is necessary to keep them alive if the starvation did not kill them. It may be necessary that such patients are managed in intensive care units judging from the many electrolyte imbalances that are not routinely checked for yet can be fatal. A high index of suspicion in adults presenting with cachexia is crucial for early identification and intervention of the appropriate care. Parenteral phosphate may be lifesaving in RFS and need to be made readily available especially in developing countries where starvation is relatively more common.

Declarations

Ethical approval and consent to participate.

Not applicable

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of supporting data

The medical records and laboratory results are available with Korle-Bu Teaching Hospital (KBTH) where he was treated.

Competing interests

We declare no conflicts of interests.

Funding

There was no funding for this study.

Authors' contributions

Dr. Eugene K Dordoye contributed to the conceptualization, writing of the methods, supervision of data and reviewing of the work. Drs. Dela Fiagbe and Josephine Stiles-Darko contributed to the management

of the patient, data analysis and review of the manuscript, Dr. Emmanuel Dziwornu and Dr Thelma M Alalbila Aku contributed to the conceptualization, writing out and reviewing of the manuscript.

Acknowledgements

We wish to acknowledge the contribution of the surviving wife and children, nurses and all other health professionals in the teaching hospital who were called in to help.

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