

# Refeeding Syndrome in Schizophrenia: a Case Report From an Emerging Economy

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## Case report

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# Abstract

## Background

Recent studies have shown growing concern for refeeding syndrome (RFS) among patients suffering other medical conditions although the exact incidence in this population is unknown. The phenomenon is also present among patients with mental health conditions characterized by poor feeding, poor appetite, catatonic features and poor cognitive functioning. Generally, RFS occurs with the reintroduction of calories to severely malnourished patients which doing so may be intuitive but life-threatening. It becomes critical for clinicians to have a high incidence of suspicion for prompt diagnosis and appropriate management to keep them alive if the poor feeding did 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. He was admitted on account of refusal to feed or drink for two weeks prior to presentation. He was severely malnourished and feeding was started while dealing with his psychotic symptoms. He gained about 2kg within a week of admission but that was fraught with metabolic derangements which included, but not limited to, hypophosphatemia, hypomagnesaemia and hypocalcaemia. We revised his diagnosis to RFS in schizophrenia and managed as such.

## Conclusion

There are no agreed biomarkers for the diagnosis of Refeeding Syndrome and diagnosis is still based on a constellation of electrolyte deficiencies and clinical presentation. Unfortunately, one of the cardinal electrolyte deficiencies, hypophosphatemia, does not have readily available formulations for its correction and this can lead to neurological, cardiovascular and other complications including sudden death. Delay in diagnosis worsens the prognosis and the intuitive desire to zealously feed a starved patient rather leads them to their death.

## Background

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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> It is potentially fatal when missed, yet there are no agreed biomarkers for diagnosis. When diagnosed, treatment can be daunting, as formulations for treatment are not readily available in developing 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”.<sup>4</sup> The syndrome can happen regardless of the route (oral, enteral or parenteral) of calorie intake.

## Case Presentation

A 53-year-old head pastor of a church living in Accra, Ghana with his wife and three children presented with a 3-month history of poor feeding, two (2) weeks of refusing to eat, and three (3) days of no water intake.

He was diagnosed and managed as schizophrenia eight (8) years prior. He improved on medication but discontinued treatment after four (4) years because his symptoms resolved. He was symptom-free for another four years and was apparently well until he began to experience symptoms that included poor personal hygiene, self-neglect and social withdrawal. It was difficult to get him help because he was a highly opinionated person. During this period, only two of his assisting pastors were permitted to visit. Two (2) weeks prior to presentation he forbade one of the two pastors from visiting.

On examination, he was severely malnourished and cachectic. He weighed 35kg with an estimated BMI of 12.5 kg/m<sup>2</sup>. An offensive body odour was noted apparently as a result poor oral and personal hygiene. He had overgrown nails (about 6cm each) and could not sit up in a wheel chair. He was negativistic and resisted any treatment. He believed his family were all against him; he consequently did not speak with any of them.

He was admitted to the psychiatry department of a teaching hospital and managed by a multidisciplinary team consisting of internists, dieticians, cardiologist, pharmacists and a neuropsychiatrist. His laboratory findings and weights during admission is as in Table 1.

Table 1

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

He was started on parenteral feeding for the first 48 hours with thiamine supplementation. Four Sub-convulsive Electrical Brain Stimulation (SCES) sessions on alternate days were initiated on day 2 of admission as patient was initially uncooperative with nasogastric (NG) tube but yielded eventually. We delivered 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 above. 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 restricted to 1000 cal/day and increased gradually to 1600 cal/day over two weeks. We observed worsening of metabolic symptoms on days that followed days he was described as “*fed well*”.

Patient developed a bilateral pneumonia on day 10 (diagnosed by x-ray) and managed on parenteral ceftriaxone and co-amoxiclav with oral azithromycin. He improved as he was able to maintain good oxygen saturation (SpO<sub>2</sub>). He however, developed right pleural effusion which yielded serous fluid on tapping on day 15. Nasopharyngeal swab was taken to rule out Covid-19; concurrently oral doxycycline, vitamin C and zinc were added to his treatment. On Day 34 he developed a high grade fever and atelectasis with bronchopulmonary fistula. He was managed with chest tube under water seal and intranasal oxygen but died suddenly two (2) days later.

## Discussion And Conclusions

Britain's National Institute for Health and Care Excellence (NICE) and Short Nutritional Assessment Questionnaire (SNAQ) have developed a screening, assessment and management guidelines to prevent RFS or mortality if it occurs.<sup>5,6</sup> However, both NICE and SNAQ have low sensitivity and specificity scores on retrospective validation analyses.<sup>4</sup> 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.<sup>7</sup>

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.<sup>8</sup> 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.<sup>9</sup>

With starvation, the body begins to break down stored glycogen and is depleted in about 72 hours. Gluconeogenesis begins from noncarbohydrate 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.<sup>10</sup> This depletion affects major organs like lung, heart, liver, intestines and kidneys with complications such as hypotension, bradycardia and hypothermia.<sup>11</sup>

The primary goal in caring for nutritionally depleted patients is the preservation of functional protein.<sup>8</sup> On resumption of feeding, glucose causes production of insulin. Insulin intrinsically enhances protein formation and prevents degradation of protein.<sup>12</sup> It pushes potassium and phosphate intracellularly for phosphorylation in glycolysis, Krebs's cycle and the electron transfer system. The resulting 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.<sup>13</sup>

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.<sup>14</sup> 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 resulting in dysfunction and death of various cell types and consequent appearance of cardiovascular and neuromuscular symptoms.<sup>15</sup>

In addition to hypophosphataemia, RFS is characterised by hypomagnesaemia, hypokalaemia, thiamine and other vitamins (B<sub>6</sub> and B<sub>12</sub>) deficiencies, trace metal deficiencies (e.g. selenium), 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 which could mask RFS symptoms.<sup>16</sup> Thiamine is required for metabolism of pyruvic and lactic acids, and links glycolysis to the Krebs's cycle. Deficiency of thiamine causes fatal acidosis.<sup>4</sup> Insulin is antinatriuretic and fluid retention occurs as a sequelae, causing death by pulmonary oedema.<sup>17</sup> These abnormalities to a greater extent explains the clinical features of RFS manifested by our patient. Table 2 depicts general clinical presentation.<sup>3</sup>

Table 2

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

A study of inpatients of an internal medicine department revealed an incidence of 8% in the study population.<sup>18</sup> 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”.<sup>4</sup> The complex metabolic changes occurs 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.<sup>4</sup> The ions implicated need to be monitored daily and replaced when low except for hyponatremia whose correction can cause pontine myelinosis.<sup>19</sup> With the poor integrity of the GI tract, parenteral replacement of the ions and the vitamins may be ideal while correcting the energy deficiency.

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. Screening for RFS should be done for all patients suspected of few weeks of poor nutrition. Parenteral phosphate can be lifesaving in RFS and should be included in the essential medicines list. More research into the incidence of RFS and the search for biomarkers is long overdue.

## Declarations

*The wife of the patient has granted permission for the history, examination and investigation findings can be used for publication once we maintain anonymity.*

*Ethical committee approval is not applicable*

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

*We declare no conflicts of interests*

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*Dr. Eugene K Dordoye contributed to the conceptualization, writing of the methods, supervision of data and reviewing of the work. Dr. Dela Fiagbe contributed to the management of the patient, data analysis and review of the manuscript, Dr. Josephine Stiles-Darko contributed to the management of the patient, data analysis and review of the manuscript, Ms. Thelma M Alalbila contributed to the conceptualization, writing out and reviewing the manuscript.*

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