Cardiac Arrest and Delirium: Presentations of the Refeeding Syndrome in Severely Malnourished Adolescents With Anorexia Nervosa

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Aim: To describe the clinical presentation of the refeeding syndrome and highlight the dangers of performing nutritional rehabilitation too rapidly in a severely malnourished patient.

Design: Retrospective case review of adolescents admitted with anorexia nervosa who developed the refeeding syndrome.

Results: Between July 1993 and July 1994, 3 of 48 adolescent females developed the refeeding syndrome. While the cardiac complications occurred in the first week of refeeding, the delirium characteristic of this syndrome occurred later and was more variably related to hypophosphatemia.

Observations: Refeeding malnourished patients with anorexia nervosa can be associated with hypophosphatemia, cardiac arrhythmia and delirium. Refeeding patients with anorexia nervosa who are <70% of ideal body weight should proceed with caution, and the caloric prescription should be increased gradually. Supplementation should be commenced early and serum levels maintained above 3.0 mg/dL. Cardiac and neurologic events associated with refeeding are most likely to occur within the first weeks, justifying close monitoring of electrolyte and cardiac status. © Society for Adolescent Medicine, 1998

Many patients with anorexia nervosa (AN) require hospitalization at some time during the course of their illness (1). The medical insurance industry and managed care companies are searching for more efficient and cost-effective ways of treating these patients, and physicians feel the pressure to refeed patients more aggressively and minimize the length of hospitalization (2).

The refeeding syndrome is a well-recognized but poorly understood syndrome characterized by sudden and unexplained death during refeeding. It is associated with cardiac and neurologic events, and death is presumed secondary to cardiac arrhythmia. It has been described in AN as well as other forms of starvation (children with kwashiorkor), patients receiving total parenteral nutrition, Japanese prisoners of war, and survivors of concentration camps in the Second World War (3).

We describe three patients who developed life-threatening complications associated with refeeding in anorexia nervosa. All of these patients were <70% of ideal body weight. The purposes of this report are to highlight clinical and laboratory markers associated with this syndrome and to remind physicians of...
the dangers of performing nutritional rehabilitation too rapidly in a severely malnourished patient.

Case 1

A 12-year-old Tanner 3 white female, who met DSM IV diagnostic criteria for AN (4) was admitted with a history of restricting food and weight loss. She lost approximately 10 lb/year for 2 years and then lost an additional 25 lb over the 2 months prior to her admission. There was no history of bingeing, purging, laxative abuse, or use of ipecac.

On admission, the patient was orientated in time, place, and person. She weighed 68 lb (61% of ideal body weight, <3rd percentile) and was 64 inches tall (75th percentile). Her examination was notable for marked cachexia. She was hypothermic (temperature 94.5°F) and moderately dehydrated (3-5%). She had lanugo, pretibial edema, and minor bruising over bony prominences. Her skin had an orange hue but no scleral icterus, consistent with carotinemia. Her pulse had a rate of 30 beats/min and was low in volume. Both heart sounds were normally heard and there was no murmur. She was normotensive (116/68 mm Hg) and without postural changes. Her abdomen was scaphoid and soft and there were no masses palpable.

Oral refeeding was initiated with 500 kcal/24 h via nasogastric tube, and total fluid intake was reduced to two-thirds maintenance (Figure 1). Initial laboratory results revealed an elevated BUN (59.0 mg/dL) but normal electrolytes including serum phosphorus (4.1 mg/dL) and alb,amin (4.5 g/dL). Sinus bradycardia and escape junctional rhythm were noted on the admission electrocardiogram (QTc 408 ms) and she was placed on cardiac telemetry. A moderate size pericardial effusion was seen on echocardiography. On Day 2, the patient became profoundly bradycardic (20–40 beats/min) and hypotensive (unrecordable by auscultation or palpation). Her body temperature was 92.9°F and capillary refill time was 3–4 s. The patient was resuscitated with fluids administered intravenously and inotropes, in the intensive care unit. The serum phosphorus had dropped to 2.4 mg/dL. Intravenous phosphate supplementation was initiated and continued orally from Day 7. On Day 8 of hospitalization she again became bradycardic and hypotensive and was transferred to the intensive care unit. Two episodes of asystolic cardiac arrest were recorded, leading to the insertion of a cardiac venous pacemaker. The serum phosphorus had dropped to 2.0 mg/dL. The echocardiographic findings remained unchanged. Subsequent serial measurements of serum phosphorus were above 3.5 mg/dL. Changes to prescribed daily calories are shown in Figure 1.

On Day 14 of hospitalization, alteration in the patient's mental status was noted. The patient described auditory and visual hallucinations. She became confused and disoriented in time and place. The patient was given haloperidol. Her delirium resolved on Day 22. Cerebral computed tomography revealed cerebral atrophy with ventricular and sulcal widening.

During hospitalization, the remainder of her serum biochemistry remained within the normal range. Thyroid function (T3 RIA 0.58 ng/mL) remained low. She received oral multivitamin supplementation. Serial echocardiographic studies revealed no change in the pericardial effusion, and ventricular function was reported to be normal throughout. By Day 25 of hospitalization, she had gained 12 lb and was receiving a total of 2800 kcal/24 h. The patient’s condition slowly improved and she was transferred to a partial hospitalization program (day hospital) at a weight of 96.2 lb (10th percentile, 86% of ideal body weight).

Case 2

A 13-year-old Tanner stage 4 white female was hospitalized following a 25-lb weight loss over five months. During this time, she had been amenorrheic and reported inducing emesis with her fingers. She met criteria for anorexia nervosa—purging type (DSM IV) (4). She denied use of ipecac or laxatives.

On admission, the patient weighed 73 lb (70% IBW, <5th percentile) and was 61.5 inches tall (25th percentile). She was cachectic with cool dry skin and lanugo. She was noted to have postural hypotension
and dehydration (≈5%). Her resting heart rate was 70 beats/min supine and 119 beats/min standing. The jugulovenous pulse was not elevated. Both heart sounds were normally heard and there was no murmur. (QTc interval was 427 ms). She was alert and orientated in time, place, and person, although her speech and locomotion were slow.

The patient was a prescribed regular diet of 1200 kcal/24 h, which was increased in increments of 100–200 kcal to 1600 kcal/24 h on Day 6. That night, a further 600 kcal was commenced by overnight nasogastric infusion. (Figure 2). On Day 7 she became acutely confused. Her delirium persisted for 7 days.

After correction of abnormal electrolytes, including low serum phosphorous, in the first week of the admission, serial biochemistry and hematology remained within normal limits. Thyroid function (T₃) also returned to the normal range.

Case 3

A 19-year-old Tanner stage 5 caucasian female presented after losing 84 lb over a 2-year period. She denied use of laxatives, diuretics, or ipecac.

On admission, she was markedly cachectic, hypothermic (91.1°F), and dehydrated (≈5%), with acrocyanosis. She weighed 82 lb (62% IBW, <5th percentile) and was 66 inches tall (75th percentile). Her skin was cool, dry, and carotinemic. She had lanugo, bruising of the lower extremities, and pitting edema to midcalf bilaterally. She was bradycardic (36/min), with a low volume pulse. Her blood pressure was 80/40 mm Hg, but there were no postural changes. The jugulovenous pressure was not elevated and both heart sounds were normally heard. Her abdomen was scaphoid and nontender. The liver edge was soft and nontender and was felt 2 cm below the costal margin in the midclavicular line. The liver had a span of 14 cm. She was alert and orientated in time, place, and person. However, both her mentation and locomotion were slow and deliberate.

Initial laboratory assessment showed normal electrolytes with the exception of low serum phosphorus (2.4 mg/dL) (Figure 3). Transaminases (AST 372 U/L and ALT 391 U/L) were mildly elevated. The serum albumin was initially in the normal range (4.0 g/dL) but did fall after rehydration (3.2 g/dL). T₃ RIA was markedly depressed (0.50 ng/mL). The patient was thrombocytopenic (34 × 10⁹/L), mildly anemic (11.1 g/dL), and leukopenic (2.1 × 10⁹/L). Her prothrombin time was elevated (INR 1.5), but the activated partial thromboplastin time was normal.

Refeeding was commenced with a prescribed regular diet of 1000 kcal/24 h. This was increased to 2200 kcal/24 h, in 200-kcal aliquots each 48–72 h. Oral phosphate supplementation was commenced on Day 5. On Day 7, the patient was confused and agitated and she described auditory and visual hallucinations. Her delirium persisted for 11 days, during which her electrolytes were normal and the transaminitis resolved. Serum ammonia on Day 10 (27 µg/dL) was within normal limits. There was a gradual increase in T₃ RIA toward the normal range.

Discussion

Anorexia nervosa occurs in 1 out of 200 adolescent girls. The resultant malnutrition has a significant morbidity and mortality (5). The earliest study of the effects of protein calorie malnutrition were by Keys et al. in 1940 (6,7), who described the effects of starvation and refeeding on male subjects (the Minnesota experiment). Medical changes in various or-
gan systems as well as a generalized metabolic disturbance affecting body composition, energy metabolism, and fluid and electrolyte status have been reported in malnourished patients with this disease (8).

Sudden death has been described in AN with refeeding, presumably from cardiac causes including arrhythmia, cardiac failure, or acute myocardial infarction (9). Both in previously published cases and in Case 1, cardiac complications occur early, usually within the first week after commencement of refeeding. Typically, but not in all cases, these clinical findings are associated with hypophosphatemia, although this is not always acknowledged (10). These findings are also more typical in patients with more severe degrees of malnutrition (<70% of ideal body weight) (11). Several authors have noted the connection with the onset of cardiac symptoms soon after commencement of total parental nutrition (12).

Fatal arrhythmia with prolonged QTc in anorexia nervosa has been described especially if the QTc was >470 ms (13). Prolonged QTc has been reported as a feature of patients hospitalized with AN, but the degree of prolongation has not been found to correlate with body mass index, suggesting that there may be other factors causing sudden death (14). These observations were well illustrated in Case 1, who was severely malnourished and in whom cardiac arrest, with concomitant hypophosphatemia but normal QTc occurred on two occasions.

While the cardiac complications occur in the first week of refeeding, the delirium characteristic of the refeeding syndrome typically occurs later (i.e., during or after the second week of refeeding) and may continue for several weeks (13,14). It is more variably related to hypophosphatemia. Yet, correction of the serum phosphate does not ameliorate the delirium. In only 2 of the 3 cases described in this study was hypophosphatemia documented.

During starvation, total body phosphorous stores are depleted, even though serum levels may be normal. The metabolic transition from catabolism to anabolism that occurs during refeeding is instrumental in precipitating a fall in serum phosphate. Intracellular influx of phosphate is stimulated by the action of insulin. Intracellular phosphate is consumed in the production of energy substrates such as adenosine triphosphate, as well as incorporated into phosphorylated intermediates required for protein synthesis and glycogen formation, and phospholipids in the cell membranes of newly forming cells (19).

Hypophosphatemia in AN may play a role in the development of both cardiac and neurologic complications (15–17). Evidence from animal experiments supports this hypothesis. Seizures, altered neurologic state (18), and marked alterations in localized central nervous system neurotransmitter levels (19) have been reported in animals studies associated with prolonged phosphate depletion. Fuller et al. demonstrated reversible myocardial depression in the dog with experimental phosphorous deficiency (20).

This hypothesis is also supported by descriptions and biochemical changes in association with hypophosphatemia in humans. These relate to reports of red cell (21), cardiac (22,23), and neuromuscular dysfunction (24–26) linked to hypophosphatemia.

Refeeding malnourished patients with AN can be associated with hypophosphatemia, central nervous system changes, arrhythmias, and sudden death. Whatever the factors involved, it is important to minimize metabolic derangements and monitor cardiac function and serum chemistries during refeeding. Accordingly, refeeding in patients with AN, especially those who are <70% of ideal body weight should be undertaken in a hospital. The initial calorie prescription should be equivalent to 130% of the resting energy expenditure as calculated by the adjusted Harris–Benedict equation or measured by indirect calorimetry (27). These patients should be observed to determine the maximum rate at which calorie prescription can be safely increased. In the first 2 weeks of treatment, serum electrolytes and phosphorus should be measured frequently. During this period, it is also preferable to have these patients monitored on cardiac telemetry because of the lack of prodromal signs for complications and sudden death during the commencement of refeeding.

References


