



## Case Report

## Refeeding syndrome in a young woman with argininosuccinate lyase deficiency☆

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## ABSTRACT

A severely chronically protein and calorie restricted young woman with argininosuccinate lyase deficiency developed transient refeeding syndrome (RFS) and hyperammonemia after modest diet liberalization following initiation of glycerol phenylbutyrate (GPB). The patient required IV supportive care and supplementation with potassium, magnesium and calcium. She is now doing well on GPB and an appropriate maintenance diet. Susceptibility to RFS should be considered in chronically nutritionally restricted patients with metabolic disorders after liberalization of diet.

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## 1. Introduction

Urea cycle disorders (UCDs) are inherited deficiencies of one of the enzymes or transporters involved in the urea cycle that converts ammonia to urea. UCDs are characterized by the accumulation of toxic levels of ammonia in the blood and brain. Medical management of UCDs is aimed at reducing waste nitrogen through restriction of dietary protein, often with amino acid supplementation [1,2] and, when necessary, use of drugs such as sodium phenylbutyrate or glycerol phenylbutyrate (GPB), which lower ammonia by enhancing excretion of waste nitrogen in the form of phenylacetylglutamine (PAGN), a urea surrogate that provides an alternative pathway for waste nitrogen excretion [3,4].

Originally described in World War II prisoners, refeeding syndrome (RFS) has more recently been recognized as comprising a wide range of typically transient, although occasionally lethal clinical and metabolic abnormalities in patients with disorders such as anorexia nervosa, cancer and gastrointestinal disease who have been inadequately nourished for as short a period as a few days [5]. During refeeding, increased blood sugar and insulin secretion result in increased glycogen, fat and protein synthesis. These metabolic processes utilize phosphate, magnesium and potassium from already depleted body stores and may result in dangerously low blood levels of these elements as well as other electrolyte abnormalities. Clinical manifestations may include severe myalgia and cardiac and respiratory difficulties [6]. We here describe RFS in a young woman with argininosuccinate lyase (ASL) deficiency.

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## 2. Case report (Table 1)

This patient, a 20-year old female, was diagnosed with argininosuccinate lyase (ASL) deficiency, a type of UCD, at 5 days of age after developing hyperammonemic coma with ammonia levels above 1000  $\mu\text{mol/L}$ . ASL activity was 0.22  $\mu\text{mol/h/g}$  Hgb (normal range: 5.5–6.5). As a result of severe recurrent hyperammonemia, she was developmentally delayed, with impaired speech, delayed gross and fine motor skills, and experienced generalized seizures effectively treated with phenobarbital. She had required hospitalization six times for hyperammonemia in the approximately 20 years since her initial diagnosis. Prior to starting GPB, her UCD was managed exclusively through diet, with arginine supplementation and protein restriction.

When seen in metabolic clinic 38 days prior to GPB treatment, the patient was noted to have lost 5.4 kg over the preceding 13 months; her BMI was 21  $\text{kg/m}^2$ . Careful history revealed that the patient's mother, fearful of hyperammonemia, had restricted her dietary protein to 26 g per day (0.4 g/kg/day), despite the physician's recommendation at the prior year's clinic visit to increase her protein to 30 g per day and to also increase her total calories. The patient's ammonia level at the clinic visit was 42  $\mu\text{mol/L}$  and, as compared with her prior visit, her serum creatinine level was down to 0.36 mg/dl from 0.51 mg/dl, and amino acids valine, isoleucine, leucine and phenylalanine were now low. Glutamine was approximately the same at 728  $\mu\text{mol/L}$  and 733  $\mu\text{mol/L}$  at the time of the clinic visit and prior visit, respectively.

The patient began treatment with GPB at 1.5 mL TID (day 0). At that time, her potassium level was 3.4 mEq/L and her ammonia level was 63  $\mu\text{mol/L}$ . Her recommended protein intake was increased to 35 g per day (0.54 g protein/kg/day) and the patient was adherent with that amount. On day 1 post GPB initiation, her GPB dose was increased to 2 mL TID and further increased to 3 mL TID on Day 19. On day 25, the

**Table 1**  
Biochemical and clinical data.

Days (On GPB)	GPB Dosing (mL TID)	Height (cm)	Weight (kg)	BMI	Protein Prescribed (g/day)	Protein Intake (g/day)	Albumin (gm/dL)	Creatinine (0.6–1.2 mg/dL)	His (38–103 μmol/mL)	Thr (34–161)	Lys (41–225)	Met (7–34)	Val (82–293)	Ile (16–89)	Leu (35–164)	Phe (25–82)	NH3 (11–35 μmol/L)	K (3.0–6.0 mEq/L)	Ca (8.5–10.5 mg/dL)
–440		172.7	69.3	23.4	45	20–21	3.4	0.51	79	52	105	29	112	22	48	36	47	3.8	9.1
–38		172.7	63.9	21.6	35	26	3.5	0.36	74	47	61	17	56	15	28	21	42	3.5	8.8
0	1.5				35	35											63	3.4	
8	2.0																111		
25	3.0				35	35	3.2								63	41	47	3.3	8.1
36	3.0				35	35	3.3	0.70					100	18			83	2.2	8.2
39	3.0				35	35											39	3.3	
44	3.0																		
59	4.0																		
130	4.0	172.9	68.2	22.9	48	48	3.7	0.40	81	37	56	14	66	19	30	22	44	4.2	9.3

Day 0: Initiation of glycerol phenylbutyrate (GPB) treatment.

Day 36: Day of admission.

Day 39: Day after release

patient's ammonia level was 47 μmol/L, her potassium level was 3 mEq/L, and she was noted to be acidotic. On that same date the mother reported that the patient was having onset of some muscle aches. By day 36, the increasingly severe muscle aches had reduced the patient to tears, and the family was encouraged to take the patient for repeat chemistry labs. Lab values at an outlying facility included potassium of 2.2 mEq/L, calcium of 8.3 mg/dL, and an ammonia of 76 μmol/L. The patient was hospitalized via the emergency room, where her ammonia level was 83 μmol/L, calcium 8.2 mg/dl, potassium 3.1 mEq/L, bicarbonate 17 mmol/L, and magnesium was 2.0 mg/dL. She was treated with intravenous fluids and discharged 2 days after admission with rapid resolution of her muscle aches, at which time her potassium was 3.2 mEq/L. The next day her phosphorus level was 4.3 mg/dL. On day 44 of GPB treatment, her potassium level was 3.6 mEq/L, calcium 8.7 mg/dL, her bicarbonate 30 mmol/L, and her phosphorus level was 5.1 mg/dL. Magnesium remained decreased at 1.6 mg/dL, requiring supplementation post discharge with magnesium oxide. On day 53, her dose of GPB was increased to 4 mL TID.

Four months after GPB initiation, the patient was ingesting 48–50 g protein per day. Her laboratory values had largely returned to normal and she was doing well on GPB while continuing with supplementation of calcium, potassium, and magnesium. Eighteen months later she has a BMI of 22.7 kg/m<sup>2</sup>, normal liver enzymes and a total protein of 7.4 g/dl. Her creatinine is still low at 0.41 mg/dl, as are her levels of phenylalanine, glutamine and branched chain amino acids. Her ammonia is 31 μmol /L. Serum PAA /PAGN ratio is (4.25mcg/mL/30.4mcg/mL) 0.14 and her urine PAGN is 20,400 mcg/ml. She was encouraged to increase her GPB dose to 4.5 ml TID so that additional small amounts of high quality complete protein could be added to her diet.

### 3. Discussion

We here describe a UCD patient who was chronically and severely protein and calorie restricted due to fear of hyperammonemic crisis. While certain features such as hypophosphatemia were not documented and the exact timing of the increase in dietary calories and protein relative to her illness is uncertain, her clinical course, including the characteristic hypokalemia, muscle aches and laboratory abnormalities that followed a period of severe protein and calorie restriction, clearly began after diet liberalization and resolved with fluid and electrolytes, appears most consistent with RFS. The patient experienced a favorable outcome due to timely recognition and appropriate management.

It is generally believed that the most important factor with respect to RFS is prevention, largely through identification of those at risk. A BMI < 16 kg/m<sup>2</sup>, unintentional weight loss > 15% over 3–6 months, little or no nutritional intake for > 10 days, and/or low levels of potassium, phosphate and magnesium are generally recognized as markers of patients at high risk for RFS [7,8]. However, these classical features were not present in this case. Instead, the patient's weight loss was comparatively modest, her BMI and albumin were at the lower end of the normal range, and the biochemical clues consisted largely of falling levels of creatinine and low branched chain amino acids. Indeed, the instructive element in this case appears to be clinically subtle historical information pertaining to chronic calorie and protein restriction.

### 4. Conclusions

These findings support the view that RFS represents a spectrum of illness [8] that should be extended to patients with inherited metabolic disorders for which dietary protein restriction is often a central component of management.

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