Risk Factors for Refeeding Hypophosphatemia in Japanese Inpatients with Anorexia Nervosa

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Abstract

Objective: Refeeding in patients with anorexia nervosa (AN) is associated with a risk of refeeding syndrome (RS), which is a disruption in metabolism with a variety of features including hypophosphatemia. We evaluated the risk factors for refeeding hypophosphatemia (RH) during nutritional replenishment in Japanese patients with AN**.** **Methods:** We retrospectively examined clinical data for 99 female inpatients (mean age 30.9 ± 10.7 years, range: 9 to 56 years). **Results:** RH (phosphate <2.3 mg/dL) occurred within 4.8 ± 3.7 days of hospital admission and was still observed at 28 days after admission in 21 of the 99 cases (21.2%). Oral or intravenous phosphate was given to some patients to treat or prevent RH. Patients with RH had a significantly lower body mass index, were older, and had higher blood urea nitrogen than those without RH. Severe complications associated with RH were recorded in only one patient who showed convulsions and disturbed consciousness at day 3 when her serum phosphate level was ~~1.5~~ 1.6 mg/dL. **Conclusion:** The significant risk factors for RH that we identified were lower BMI, older age, and higher blood urea nitrogen at admission. No significant difference in total energy intake was seen between the RH and no RH groups, suggesting that RH may not be entirely correlated with energy intake. Precisely predicting and preventing RH is difficult, even in patients with AN who are given phosphate for prophylaxis. Thus, serum

phosphate levels should be monitored for at least 5-10 days after admission.

Introduction

Anorexia nervosa (AN) is a ~~lifelong~~ Life-threatening illness with frequent relapses[1]. According to surveys of 10,499 Japanese female students in 1982, 1992, and 2002, the point prevalence of AN has dramatically increased from 0.11% in 1982 to 0.43% in 2002[2]. Effective treatment of patients with AN always starts with nutritional rehabilitation and weight restoration. However, insufficient research in the field of refeeding malnourished patients has resulted in a lack of consensus and ambivalence about the appropriate initial refeeding intake, and consequently, refeeding practices remain inconsistent[3,4]. The main safety concern in treating AN is refeeding syndrome (RS), which is a disruption in metabolism characterized by hypophosphatemia, hypomagnesemia, hypokalemia, and hypoglycemia[5]. In its most severe form, RS is associated with cardiac arrhythmia, delirium, and sudden death. RS can be treated or prevented with early diagnosis and a slow rate of refeeding[6].

Refeeding hypophosphatemia (RH) is typically used as a surrogate for RS[5]. The rate of ~~RH in patients with AN ranges widely from 14% in adolescents[7] to 45% in adults[8]~~. RH range varies from 0% to 45%. (19, 20, 21) Common practice involves beginning with low-

energy intake that is increased slowly to avoid RH. However, very low energy intake can lead to insufficient weight gain[9]. The severity of malnutrition is a better predictor of the development of RH than total energy intake in adolescents[7]. The severity of malnutrition (%mBMI: percentage median body mass index for age-and-sex; average 77.9%) is a better predictor of the development of RH than total energy intake in adolescents[7]. However, no clinical features predict RH in adults including admission body mass index (BMI) and initial amount of energy intake[8]. The most important issue concerning RH prevention is predicting its occurrence from risk factors, because RH onset can be very rapid, sometimes within ~~hours~~ days (22, 23, 24). The aim of this study was to evaluate the risk factors for RH during nutritional replenishment in a sample of Japanese inpatients with AN.

Materials and Methods

A total of 126 admissions (N = 72 participants) of patients with AN (seven men [5.6%] and 119 women [94.4%]) consistent with ICD-10 diagnostic criteria occurred to the psychiatric ward in Tokushima University Hospital from January 2006 through December 2013. The Institutional Review Board approved the study. Ultimately, 99 (N = 61 participants) of the 126 (78.6%) admissions with AN who were female and whose BMI was under 17.5 kg/m^2 were enrolled in the study. Because %mBMI in 11 cases of adolescents (54.8%~84.1%) was significantly correlated with their absolute BMI (r=0.773 p=0.005, Spearman correlation

test), we applied absolute BMI for both adolescents and adults. The mean age of the patients at their initial hospitalization was 30.9 ± 10.7 years (range: 9 to 56 years). The mean length of stay in the hospital was 82.7 ± 77.8 days (range: 1 to 312 days). The enrolled patients were examined and diagnosed by individual consultant psychiatrists in our department. Their diagnoses at intake were also checked by various psychiatrists during a conference. A retrospective chart review was independently conducted by at least two trained psychiatrists (N.K. and J.I.).

Data were extracted from paper and electronic medical records. We documented the reason for admission, relevant medical history, demographics, and anthropometric and clinical data at hospital admission. Energy intake (kcal), liquids, and electrolyte substitutions were recorded for the duration of the hospital stay. Basically, we used low-calorie approach. Total energy intake at admission refers to the average total energy intake from day 1 through day 7. We consulted about the amount of energy intake with the nutrition support team depending on the amount of energy intake just before admission, blood test data and patient's acceptance in acute phase treatment. Mean energy intake was increased to over 1500kcal/day at discharge in most cases.

Hematologic and biochemical analyses were performed in the hospital's central laboratory with standard methods and reference measurements. Laboratory data were evaluated from

days 1 through 28. The Student's *t*-test was used for analyses. $P < 0.05$ was considered to be significant.

Results

Patient characteristics

During the 28-day follow-up, RH (phosphate <2.3 mg/dL) was observed at least one time in 21 of the 99 cases (21.2%). The mean time between admission and occurrence of RH was 4.8 ± 7.7 days. Among patients with RH (N = 21), 16 patients (76.2%) received phosphate orally or intravenously to treat the hypophosphatemia, and four patients (19.0%) received phosphate for 9.6 ± 6.9 days for prophylaxis. We used prophylactic phosphate when patients were admitted to the hospital on the weekend, because we could not examine the serum phosphate level on the weekend. Among patients without RH (N = 78), eight patients (10.3%) received phosphate for 7.4 ± 7.8 days for prophylaxis. A comparison of clinical variables in patients with and without RH is presented in Table 1. Patients with RH were characterized by a significantly lower BMI, older age, and higher blood urea nitrogen (BUN) at admission. The groups did not differ regarding any other characteristics including total energy intake at admission. Binominal regression analysis that include age at admission, BMI at admission and BUN/Cre ratio revealed BUN/Cre ratio was remained to be statistically significant (Odds Ratio:1.062, 95% C.I: 1.019-1.106).

Redgrave et al found that there was no association between age and RH in their binomial regression model that included age, sex, admission BMI, inpatient rate of weight gain, and whether or not the patient had multiple admissions to the program during the study period. The difference in findings may come from not only BMI but also other physical co-morbidities in severe AN.

Time course of RH

The mean and minimum serum phosphate levels in the RH group and the no RH group are depicted in Figures 1, respectively. RH occurred at 4.8 ± 3.7 days after admission. Five patients in the RH group showed hypophosphatemia at admission. Two patients in the RH group were first admitted to the internal medicine ward without checking serum phosphate levels and were then transferred to the psychiatric ward and found to have hypophosphatemia. Among patients whose serum phosphate levels were checked at admission, the first day at which hypophosphatemia was observed ranged from day 1 to day 10. All RH cases including the two patients who were first admitted to the internal medicine ward had recovered by day 19.

RH-related complications

In the RH group, severe complications associated with RH were recorded in only one patient. The 50-year-old patient (BMI: 10.6 kg/m^2) showed convulsions and disturbed

consciousness at day 3 when her serum phosphate level was 1.6 mg/dL. The lowest serum phosphate level (0.3 mg/dL) in this series of patients was observed in a 30-year-old patient (BMI: 9.7 kg/m^2). In this patient, hypophosphatemia was found with a regular blood test in the outpatient clinic, and the patient was transferred to the psychiatric ward on the same day. She was conscious and alert and showed no subjective symptoms. For several days before her regular visit, she increased her energy intake to avoid involuntary admission. Her hypophosphatemia had recovered by day 6.

Discussion

A recent review[7] identified a wide range in refeeding rates (125-1900 kcal/day), which may be due to the unpredictable presentation of RH coupled with insufficient research into interventions in the area of refeeding malnourished patients. The absence of data has hindered the development of comprehensive global refeeding guidelines. A noticeable difference is seen in proposed guidelines for refeeding rates adopted in Europe and Australia compared to North America. The European and Australian guidelines recommend that refeeding commence more conservatively than American recommendations: 5-20 kcal/kg[10,11] and 30-40 kcal/kg[12], respectively. The recommended refeeding guidelines were based on clinical experience rather than scientific evidence. In this study, total energy intake was within the recommended rate, and no significant difference between the RH

group and no RH group was seen. Our result suggests that RH may not be entirely correlated with energy intake.

The significant risk factors for RH that we identified in our study were lower BMI, older age, and higher BUN at admission. Many studies have reported that the lowest refeeding phosphate level is directly proportional to malnutrition[13,14,15]. A recent systematic review also indicated that the severity of malnutrition was a better marker for the development of RH than total energy intake[7].

To the best of our knowledge, this is the first report showing that older age may be a risk factor for RH. In general, older patients have a longer illness duration, longer-term malnutrition, and more physical complications. Age-related impairment of physical function or low reserve function caused by the longer disease duration may be associated with this result. The estimated time of illness of the 99 patients in our study was 10.8 ± 8.4 years and was significantly correlated with the age at admission ($r = 0.76$, $P < 0.05$, Spearman correlation test). All patients whose estimated time of illness was less than 1 year (n = 6) did not present with hypophosphatemia. Although chronicity was thought to be protective from RS due to malnutrition adaptation, age-related impairment of physical function or low reserve function caused by a longer disease duration may be associated with this result. (16, 17, 18)

Higher BUN and BUN/Creatine ratio may be risk factors for RH. Dehydration is suggested if the BUN/Cre ratio is above 10. At admission, 80% of the patients in our study had a BUN/Cre ratio above 10, and intravenous dripping promptly decreased their BUN and Hematocrit. Thus, a higher BUN or BUN/Cre ratio seems to be associated with dehydration. In this study, BMI and the BUN/Cre ratio at admission were negatively correlated ($r = -0.61$, $P < 0.001$). Dehydration and severe malnutrition often co-exist in severe AN. Consistent with this result, drastic malnutrition such as unintentional weight loss greater than 15% ~~over the previous 3-6 months~~ body weight lost and little or no nutritional intake for more than 10 days renders a patient at high risk for developing refeeding problems, according to the National Institute for Health and Care Excellence (NICE) guidelines (25).

The observation that RH occurred at 4.8 ± 7.7 days after admission is important. As far as we know, no clinical recommendations exist for the follow-up period of RH. According to our result, follow-up measurement of serum phosphate may be necessary for ~~at least 5-10 days~~ more than 5 days in patients with AN at high risk for RH.

The main limitation of our study is that patients were retrospectively studied. The present findings are limited to severe, hospitalized cases and therefore cannot be generalized to outpatient or community samples. We did not examine other complications

of RS such as hypomagnesemia, hypokalemia, and hypoglycemia. Finally, treatment was not controlled for this study, and patients received a variety of treatments during follow-up.

Conclusion

Our data indicate that lower BMI, older age, and higher BUN (dehydration), but not total energy intake, at admission are significant risk factors for RH. Because precisely predicting and preventing RH is difficult, even in patients with AN who are given phosphate for prophylaxis, serum phosphate levels should be monitored for ~~at least 5-10 days~~ more than 5 days after admission.

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Table 1. Comparison of clinical variables in patients with and without refeeding hypophosphatemia.

		RH group (N = 21)	No RH group (N = 78)	P value
BMI at admission (kg/m^2)		11.00 ± 2.34	13.17 ± 2.24	0.000
Age at admission (years)		36.0 ± 8.4	29.5 ± 10.8	0.012
Total energy intake (kcal/day)		858.8 ± 353.5	841.8 ± 447.7	0.876
	Normal range			
Na (mEq/L)	135-146	136.0 ± 5.9	136.4 ± 6.2	0.821
K (mEq/L)	3.5-4.8	3.51 ± 0.62	3.76 ± 1.18	0.379
Cl (mEq/L)	98-108	94.2 ± 14.6	91.7 ± 16.2	0.560
Ca (mg/dL)	8.8-10.1	8.75 ± 1.05	9.21 ± 0.75	0.057
Mg (mg/dL)	1.6-2.3	2.25 ± 0.50	2.22 ± 0.33	0.777
P (mg/dL)	2.4-4.6	3.46 ± 2.16	4.51 ± 2.23	0.109
RBC (10^6/μL)	3.90-4.90	3.788 ± 0.763	3.955 ± 0.792	0.427
HGB (g/dL)	11.5-14.5	11.94 ± 2.34	11.87 ± 0.39	0.913
HCT (%)	34-43	34.71 ± 6.28	35.17 ± 6.57	0.791
AST (U/L)	10-35	166.0 ± 216.9	80.8 ± 162.6	0.121
ALT (U/L)	5-40	133.4 ± 204.7	69.3 ± 154.1	0.150
γ-GTP (U/L)	0-30	74.1 ± 77.9	75.4 ± 152.7	0.972
FBS (mg/dL)	60-110	76.8 ± 40.1	77.5 ± 40.3	0.945
ALB (g/dL)	3.9-4.9	3.25 ± 0.71	3.68 ± 0.80	0.063
BUN (mg/dL)	8-20	31.5 ± 15.9	21.3 ± 17.4	0.027
Cre (mg/dL)	0.4-0.9	1.043 ± 1.264	1.492 ± 2.018	0.357
BUN/Cre	-	45.03 ± 28.18	19.87 ± 12.26	0.001

Student's t-test was used for analyses. The data are the mean ± standard deviation. Abbreviations: Na: Sodium, K: Potassium, Cl: Chloride, Ca: Total calcium, Mg: Magnesium, P: Phosphate, RBC: Red blood cells, HGB: Hemoglobin, HCT: Hematocrit, AST: Aspartate transaminase, ALT: Alanine transaminase, γ-GTP: Gamma glutamyl transferase, FBS: Fasting blood sugar, ALB: Albumin, BUN: Blood urea nitrogen, Cre: Creatinine, BUN/Cre: BUN creatinine ratio

Figure 1. Mean and minimum serum phosphate level in the RH group (A) and the No-RH

group (B) during the first 28 days after admission.