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ORIGINAL

Hyperemesis gravidarum followed by refeeding syndrome causes electrolyte abnormalities induced rhabdomyolysis and diabetes insipidus

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Abstract. Although hyperemesis gravidarum (HG), an extreme form of morning sickness, is a common complication during pregnancy, HG associated simultaneous onset of rhabdomyolysis and diabetes insipidus due to electrolyte abnormalities are rare. A 34-year-old woman with severe HG at 17 weeks of gestation complicated with appetite loss, weight reduction by 17 kg, general fatigue, myalgia, weakness and polyuria was identified to have simultaneous hypophosphatemia (1.6 mg/dL) and hypokalemia (2.0 mEq/L). Appetite recovery and the improvement of the hypophosphatemia (3.2 mg/dL) were observed prior to the first visit to our department. At the admission, she presented polyuria around 7,000~8,000 mL/day with impaired concentrating activity (U-Osm 185 mOsm/L), and abnormal creatine kinase elevation (4,505 U/L). The electrolyte disturbances and physio-metabolic abnormalities in undernourished state due to HG let us diagnose this case as refeeding syndrome (RFS). In this case, abnormal loss by vomiting, insufficient intake and previous inappropriate fluid infusion as well as the development of RFS may accelerate the severity of hypokalemia due to HG. Thus, as her abnormalities were considered as results of rhabdomyolysis and diabetes insipidus due to severe HG associated hypokalemia based on RFS, oral supplementation of potassium chloride was initiated. After 6 days of potassium supplementation, her symptoms and biochemical abnormalities were completely resolved. Severe HG followed by RFS can be causes of electrolyte abnormalities and subsequent complications, including rhabdomyolysis and renal diabetes insipidus. Appropriate diagnosis and prompt interventions including adequate nutrition are necessary to prevent electrolyte imbalance induced cardiac, neuromuscular and/or renal complications.

Key words: Hyperemesis gravidarum (HG), Refeeding syndrome (RFS), Hypokalemia, Rhabdomyolysis, Diabetes insipidus (DI)

HYPEREMESIS GRAVIDARUM (HG) is one of a common cause of hospitalization in early pregnancy [1, 2]. Nausea and vomiting afflict up to 50–80% of pregnancies, with the more serious form, HG, complicating approximately 0.2–3.6% of pregnancies [1]. As there is no international consensus on the definition of HG, this syndrome has been a clinical diagnosis made after other causes of vomiting and nausea have been excluded [1]. According to the newly published systemic review, vomiting, nausea, gestational age, ketone urea/acidosis and need for hospitalization are major definition criteria for HG [1]. HG associated intractable vomiting as well as anorexic condition can lead to severe dehydration, significant weight loss and electrolyte imbalance including hypokalemia [3]. HG also causes prolonged starvation and may develop poorly nourished state. Upon nutritional therapy or even under natural oral intake in those situations, refeeding syndrome (RFS) can develop in short period of time (2~3 days), encompassing severe electrolyte disturbances (hypophosphatemia, hypokalemia, and hypomagnesemia), and physio-metabolic abnormalities [4].

Potassium homeostasis typically remains normal in pregnancy despite multiple physiologic changes that promote renal potassium wasting: volume expansion, increased renal blood flow, increased glomerular filtration rate (GFR), elevation of cortisol levels and activation of the renin-angiotensin-aldosterone (RAS) axis. Serum potassium levels are maintained at physiologic levels by increased levels of progesterone, which resist

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kaliuresis [5]. This compensatory mechanism can be easily overwhelmed by maternal conditions such as gastrointestinal disorders, alcoholism, malnutrition, diabetes mellitus, and tubulointerstitial disorders and can lead to maternal hypokalemia. Around 40% of the women suffered from HG had hypokalemia, while 36% and 8% of those had hyponatremia and hypochloremia, respectively [6].

Although the pathophysiological causal relationship is understandable, only two cases with simultaneous onset of rhabdomyolysis and diabetes insipidus (DI) due to HG associated hypokalemia have been reported [7, 8]. We herein describe a rare and instructive case of HG followed by RFS associated hypokalemia induced rhabdomyolysis and nephrogenic DI, successfully treated with oral supplementation of potassium chloride tablets.

Case Presentation

A 34-year-old woman, gravida 5, para 1, was conceived in a natural cycle. She had been complaining of severe nausea and vomiting for a while, and visited a local clinic on mid- February 20XX, and was diagnosed as 4–5 weeks of pregnancy. She still had excessive vomiting, thus she admitted to the clinic and was managed conservatively with intravenous infusion of fluids (glucose lactated Ringer's solution. glucose 50.0 g/L. Na^+ 131.0 mEq/L. K^+ 4.0 mEq/L. Cl^- 110 mEq/L, Ca^{2+} 3.0 mEq/L. calorie 200 kcal/L. 1,500 mL/day). Despite this intervention, her vomiting and nausea were not resolved, and her body weight was decreased from 69 kg to 52 kg (BMI = 19.1), indicating that her body weight reduced by 17 kg (–24.6%) in 12 weeks. She has been hospitalized in the clinic from Feb. 22nd to Apr. 4th. As her general fatigue, myalgia, muscle weakness and appetite loss appeared to be progressive, she was transferred to the Department of Obstetrics and Gynecology in our hospital on April 23rd 20XX at 17 weeks and 2 days of gestation. Of note, she started to recover her natural appetite around mid-April, and those symptoms became even worse.

At the first visit, she complained polyuria around 7,000~8,000 mL/day with impaired concentrating activity (U-Osm 185 mOsm/L), and the biochemical examination revealed that she had hypophosphatemia (1.6 mg/dL), hypokalemia (2.0 mEq/L) and abnormal creatine kinase (CK) elevation (4,505 U/L). Although arterial blood gas was not sampled, elevation of the difference between sodium and chloride (Na-Cl = 139 – 98 = 41 > 40) suggested that she had metabolic alkalosis. No obvious electrocardiogram changes, such as long QTc intervals, flatted T wave or U wave were observed. Her fetus was growing appropriately.

Thus, she was consulted to the Department of Diabetes, Metabolism and Endocrinology for further diagnostic studies. Urinary potassium to creatinine ratio (3/0.389 = 7.712 < 13 mEq/gCre) indicated that the renal potassium loss was not compatible. Serum glucose, magnesium, thyroid function and RAS system were not in the abnormal range.

A history of paralysis, thyrotoxicosis, use of insulin or β-agonist was not detected. Hypophosphatemia was obvious on Apr. 23rd (IP 1.6 mg/dL), but was quickly resolved at 3.2 mg/dL in two days without any replacement therapy.

According to these clinical courses, the primary pathophysiological situation can be explained by refeeding syndrome (RFS) on severe undernourished state due to HG, resulting in electrolyte disturbances such as hypophosphatemia and hypokalemia, rhabdomyolysis and nephrogenic DI. Therefore, less intake and excessive loss of potassium due to severe HG followed by RFS was considered as causes of her hypokalemia. Trial administration of oral Desmopressin Acetate Hydrate (120 μg tablet. twice a day) for two days was implemented, but did not work to reduce the amount or to concentrate her urine. Because hypophosphatemia was spontaneously resolved, and hypokalemia may evoke both polyuria and rhabdomyolysis simultaneously, we primarily attempted to correct her potassium levels.

In such severe hypokalemia, intravenous infusion of appropriately diluted potassium is recommended to control serum potassium levels, however, she refused to be operated infusions because she was suffered from previous intravenous treatments. Then, she was firstly treated with sustained-release potassium chloride tablets (48 mEq/day. Fig. 1). At the same time, her appetite became more recovered. After 6 days of potassium supplementation, her symptoms such as general fatigue, myalgia and muscle weakness were totally resolved. The amount of urine became reduced to 2,100 mL with appropriate concentration (U-Osm 561 mOsm/L. Table 1. Fig. 1). Both hypokalemia and rhabdomyolysis were also completely normalized (K: 4.1 mEq/L. CK: 49 U/L. Table 1. Fig. 1). After confirmation of her fully recovered appetite, potassium supplementation was ceased, and her potassium levels were sustained thereafter (Fig. 1).

At the end of Sep, 20XX, she gave birth to a 3,065 g of female newborn at 39 weeks of gestation with both one and five minute Apgar score of 9/10. Her serum phosphate, potassium, CK levels and urine output were normal during perinatal period.

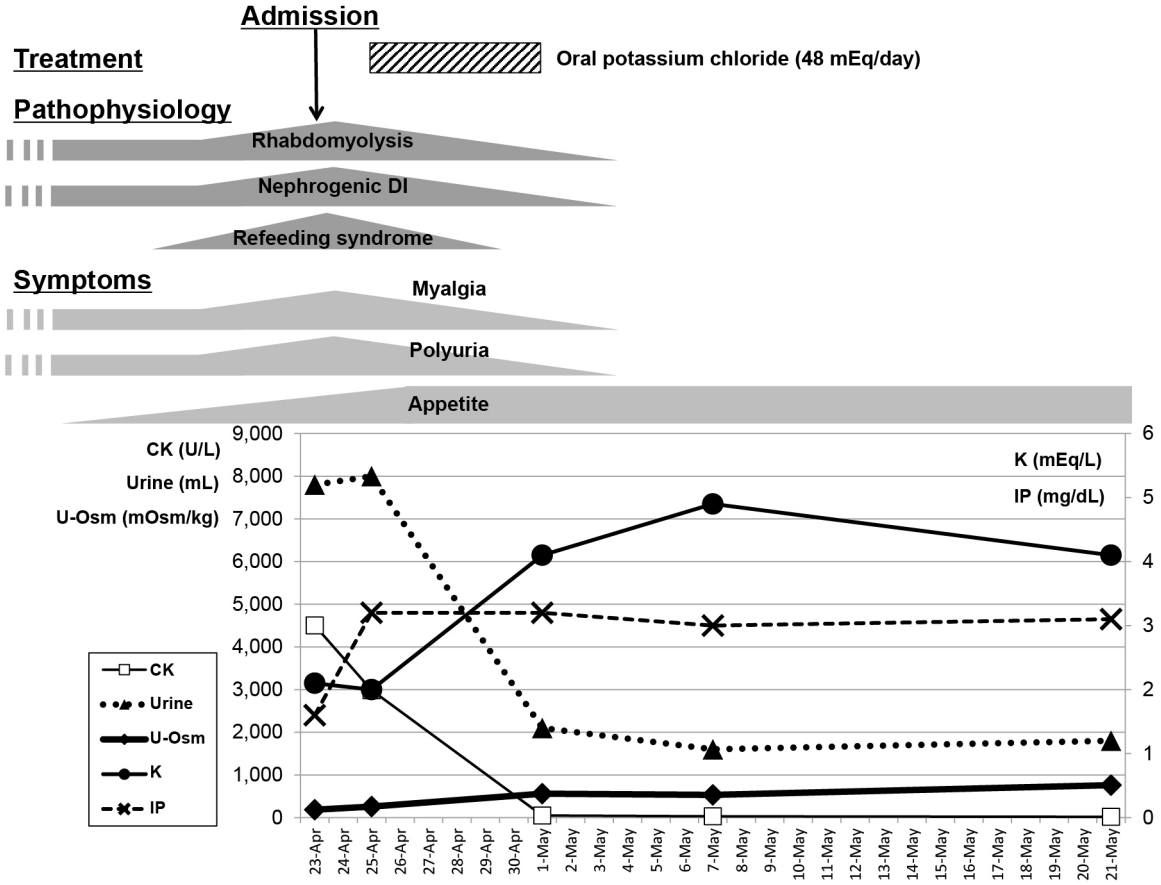

Fig. 1 Clinical timeline of this patient.
Upper panel indicates the chronological changes in treatment, pathophysiology and symptoms. Lower panel shows the time course of biochemical and physiological data in this patient.

Discussion

Hyperemesis gravidarum (HG)

Hyperemesis gravidarum (HG) is one of the common complications of early pregnancy. In a large population-based cohort study [9], HG was not associated with an increased risk of long-term all-cause mortality [10] and no increase in mortality due to cardiovascular disease, however, secondary to HG induced hypokalemia and/or hypomagnesemia may cause ventricular tachycardia in a pregnant patient with a structurally normal heart [11, 12]. Indeed, hypokalemia is associated with emergency operative delivery (adjusted odds ratio: 2.7) [10]. It would be rare, but HG is also related to osmotic demyelinating syndrome due to hyponatremia [13], Wernicke's encephalopathy due to vitamin B1 (thiamine) deficiency [14] and hypokalemic myopathy [7, 8]. Although intravenous treatment strategy is not established, it is reported that intravenous rehydration with 5% dextrose–0.9% saline or 0.9% saline solution in women hospitalized for HG produced similar outcomes [15].

Refeeding syndrome

Refeeding syndrome (RFS) represents wide variety of clinical symptoms and electrolyte abnormalities in severely mal-nourished patients [4, 16]. Clinical manifestations of RFS develop when those patients are initiated with nutritional supplementation *via* oral, enteral or parenteral routes. Multiple organ systems including cardiac, respiratory, neurologic, and hematologic can be damaged and may lead to multisystem organ failure and death in the most severe of cases. The major findings in RFS are fluid and electrolyte imbalance, including hypophosphatemia, hypokalemia, hypomagnesemia and others. This case presented the worsening of symptoms after natural appetite recovery. Hypophosphatemia and hypokalemia were identified soon after the episode. Indeed, occurrence is mostly within the first 72 h of start nutritional therapy [4]. This case meets the criterion, such as "unintentional bodyweight loss more than 15% (–24.6% in this case) in the preceding 3 to 6 months", "minimal or no significant nutritional intake for more than 10 days (12 weeks in this case)" and "low concentrations of plasma potassium (2.0 mEq/L in this case), phosphate

Table 1 Biochemical examinations in pre and after the oral potassium treatment of hypokalemia

	Apr. 23rd	Apr. 25th	May 1st
TP (g/dL)	5.3	4.7	6.5
Alb (g/dL)	2.9	2.4	3.7
Na (mEq/L)	139	141	136
K (mEq/L)	2.1	2.0	4.1
Cl (mEq/L)	98	103	104
Ca (mg/dL)	7.8	7.8	
IP (mg/dL)	1.6	3.2	3.2
Mg (mg/dL)	2.4	2.4	2.4
UA (mg/dL)		2.3	3.2
BUN (mg/dL)	2.6	2.2	4.6
Cre (mg/dL)	0.3	0.29	0.34
eGFR (mL/min/1.73 m^2)	>90	>90	>90
Glu (mg/dL)	102	69	73
HbA1c (%)	5		
s-Osm (mOsm/kg)	265	267	259
T-Bil (mg/dL)	0.4	0.3	0.3
D-Bi (mg/dL)		0.1	0.1
AST (U/L)	135	187	51
ALT (U/L)	90	133	117
LD (U/L)	333	305	264
CK (U/L)	4,505	2,987	49
CK-MB (U/L)		43	9
Fe (μg/dL)		108	
UIBC (μg/dL)		76	
T-CHO (mg/dL)	168	168	168
TG (mg/dL)	297	280	297
HDL-C (mg/dL)	41	38	41
LDL-C (mg/dL)	93	90	93
T-keton (μmol/L)		194.3	94.2
AcAc (mmol/L)		59.9	23
3-OHBA (mmol/L)		134.4	71.2
U-Crea (mg/dL)	31.1	38.9	65.7
U-Na (mEq/L)	42	93	128
U-K (mEq/L)	3	3	70
U-Cl (mEq/L)		74	195
U-Osm (mOsm/kg)	185	260	561
ADH (pg/mL)	1.6		0.9
TSH (μIU/mL)	2.98	4.09	
FT3 (pg/mL)	2.97	3.36	
FT4 (ng/dL)	0.8	0.88	
ACTH (pg/mL)		34.21	
cortisol (μg/dL)		9.1	
DHEA-S (μg/dL)		21	
PRA (ng/mL/h)		2.8	
PAC (pg/mL)		<10.0	
GH (ng/mL)		3.4	
IGF-1 (ng/mL)		130	
LH (mIU/mL)		<0.1	
FSH (mIU/mL)		0.1	
PRL (ng/mL)		149.2	
HCG (mIU/mL)		12,805	
E2 (pg/mL)		2,415	
Prog (ng/mL)		28.3	
WBC (/μL)	10,600	7,800	8,000
RBC (×10^6/μL)	4.34	3.72	4.2
Hb (g/dL)	12.6	11	12.3
Hct (%)	36.2	32.5	39.1
PLT (×10^6/μL)	239		249

PRA: Plasma renin activity
PAC: Plasma aldosterone concentration

(1.6 mg/dL in this case) or magnesium" [17]. The recommended approaches of preventing or treating RFS were the following: recognizing the patients at risk; providing adequate electrolyte, vitamin, and micronutrient supplementation; careful fluid resuscitation; cautious and gradual energy restoration; and monitoring of critical laboratory indices [16].

Hypokalemia

Hypokalemia is clinically common, which occurs in up to 21% hospitalized patients and 2–3% of outpatients [18]. Serum potassium concentration is closely regulated by a variety of mechanisms. Potassium is predominantly an intracellular cation, as only 2% of the total body potassium can be found the extracellular space. The homeostatic serum potassium concentration is maintained by the terminal nephron segments of the kidney. Insulin, β-adrenergic agonists, aldosterone and a change in blood pH may all independently affect the serum potassium levels. Hypokalemia results from abnormal losses, transcellular shifts and/or insufficient intake [18]. Abnormal losses such as renal loss or gastrointestinal loss are most common. In this case, abnormal loss by vomiting, insufficient intake and inappropriate fluid infusion as well as RFS associated intracellular shift may accelerate the severity of hypokalemia due to HG.

In case of hypokalemia due to HG, hypovolemia may co-exist, which in turn activates RAS system to maintain physiological volume. When this happens, hypokalemia may be further enhanced by kaliuresis due to the effect of aldosterone. But in this case, RAS activation was not observed (aldosterone <10 pg/mL), may be due to previous intravenous infusion therapy. In this context, intravenous infusion of fluids with appropriate electrolytes should be primarily important, but volume corrections alone may have contributed to minimizing potassium loss by preventing the excessive RAS activation in this case.

The immediate goal of the management of hypokalemia is the prevention of potentially life-threatening cardiac conduction disturbances and neuromuscular dysfunction including rhabdomyolysis by correction of serum potassium to a safe level. In this case, both rhabdomyolysis and polyuria were speculated as consequences of hypokalemia due to HG, supplementation of potassium was firstly chosen whether these abnormalities could be ameliorated. As serum potassium concentration decreases approximately 0.3 mEq/L for every 100 mEq reduction in total body potassium, the potassium deficit in this case was estimated approximately 500 mEq. Because the patient gradually started meals and refused to use intravenous infusions, the potassium correction was initiated by oral potassium chloride tablets (48 mEq/

day). Indeed, non-urgent hypokalemia is treated with 40 to 100 mEq of oral potassium over days to weeks.

Nephrogenic diabetes insipidus

DI is a rare complication of pregnancy. Pregnancy specific DI has been known as gestational DI, which is caused by an overexpressed placental vasopressinase [19] and usually appeared in the third trimester.

Polyuria occurred secondary to nephrogenic DI as a consequence of severe hypokalemia in this case. Indeed, hypokalemia is a common electrolyte imbalance that can cause a defect in urinary concentrating ability, *i.e.*, nephrogenic DI. When serum potassium level drops, water channel aquaporin-2 is reduced by enhanced autophagic degradation [14], thus results in impaired sensitivity to antidiuretic hormone, and subsequent aquaresis. Indeed, this case did not respond Desmopressin Acetate Hydrate tablet, but this nephrogenic DI can be quickly resolved by the correction of potassium levels.

Rhabdomyolysis

Rhabdomyolysis is the destruction of a significant amount of striated muscle, leading to disruptions in fluid balance, electrolytes and renal function. Diagnosis is typically made through the timely determination of the serum CK in a patient with a suggestive history or clinical features. The most frequent symptoms of rhabdomyolysis are fatigue, weakness, myalgia and swelling, although it is possible that some patients are completely asymptomatic.

The common and well-known causes of rhabdomyolysis include excessive physical exercise, trauma, alcoholism, medications (such as statins, and β-stimulants for the pregnant woman who has myotonic dystrophy), liquorice (herbal medicine), certain genetic disorders and electrolytes disorders such as hypokalemia. In the pregnant women with myotonic dystrophy, ritodrine-induced rhabdomyolysis has been reported [20]. Muscle destruction due to rhabdomyolysis causes the release of large amounts of potassium in the circulation. Consequently, when rhabdomyolysis develops in the situation of hypokalemia, the apparent concentration of potassium may appear to be slightly low to normal range. Therefore, the absolute potassium levels could be lower than the data indicated.

Conclusion

Severe HG followed by RFS can be causes of electrolyte abnormalities and subsequent complications, including rhabdomyolysis and nephrogenic DI. Clinical attention should be paid on severe HG having potential RFS risks, resulting in hypokalemia accompanied by CK elevation and polyuria.

Disclosure

The authors declare that they have no conflicts of interest to disclose.

Author's Contributions

T.K., M.N., and M.Y., took care of the patient. T.K., and T.O. wrote the manuscript. J.K., T.M., H.K., and E.A. contributed discussion.

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