대한소아신장학회지 제 14 권 제 2 호 2010년
DOI 10.3339/jkspn.2010.14.2.230

□증 례□

Hypokalemia-induced Polyuria with Nocturia after Intravenous Methylprednisolone Pulse Therapy in a Henoch-Schönlein Purpura Nephritis Patient

Geun Jung Kim, M.D. and Jun Ho Lee, M.D.

Department of Pediatrics, CHA University, CHA Bundang Medical Center

= Abstract =

Patients with moderate to severe degrees of Henoch-Schönlein purpura (HSP) nephritis receive high-dose intravenous methylprednisolone pulse therapy (IMPT). Although the regimen is generally safe and effective, various complications occasionally develop. administration of excessive corticosteroid can induce urinary potassium wasting leading to hypokalemia. Polyuria, one of the complications of hypokalemia, is related to both increased thirst and mild nephrogenic diabetes insipidus. And hypokalemia itself also impairs the maximal renal urinary concentration ability. Although polyuria or nocturia after IMPT is not common, it is correctable immediately by oral potassium supplementation. Therefore, during IMPT, careful history taking of nocturia as well as monitoring urine volume, serum and urine potassium level at regular follow-up are necessary because even mild hypokalemia can provoke urine concentrating ability defect. We experienced a case of 11 year-old boy with HSP nephritis who suffered from hypokalemia-induced polyuria with nocturia right after IMPT. (J Korean Soc Pediatr Nephrol 2010;14:230-235)

Key Words : Methylprednisolone pulse therapy, Hypokalemia, Polyuria, Nocturia, Henoch-Schönlein Purpura nephritis

Introduction

High dose intravenous methylprednisolone pulse therapy (IMPT) has been used for the treatment of moderate to severe degrees of Henoch-Schönlein purpura (HSP) nephritis [1]. Patric and Renée reported that 38 children with HSP received high dose methylprednisolone therapy at a dose of 1,000 mg/1.73m^2 three pulses every other day [6]. Also, the therapy is often used in several rheumatologic conditions such as systemic lupus erythematosus, rheumatoid arthritis, and pemphigus vulgaris and also in treatment for acute rejection after organ transplantation [3-5]. However, it has been associated with several adverse effects including hypertension, arrhythmias such as sinus bradycardia, atrioventricular block, atrial fibrillation, atrial flutter, and ventricular tachycardia, gastrointestinal troubles such as nausea and

접수 : 2010년 8월 6일, 수정 : 2010년 8월 26일
승인 : 2010년 9월 3일
책임저자 : 이준호, 경기도 성남시 분당구 야탑동 351
차의과대학교 분당차병원 소아청소년과
Tel : 031)780-6511 Fax : 031)780-5011
E-mail : naesusana@yahoo.co.kr

vomiting, cataracts, hypokalemia, and infections [2, 5].

Herein we report our experience with an 11-year-old boy who suffered from nocturia and polyuria after receiving high-dose IMPT because of moderate degrees of HSP nephritis.

Case report

An 11-year-old boy was diagnosed with Henoch-Schönlein purpura (HSP) one week ago was admitted for renal biopsy because microscopic hematuria and nephrotic range of proteinuria had developed. There were no remarkable findings on past medical history and family history. His blood pressure was 100 mmHg systolic and 60 mmHg diastolic. Heart rate was 80 beats/min and body temperature was 36.8℃. He weighed 30.2 kg (10-25th percentile) and was 140 cm tall (25-50th percentile). Laboratory findings at admission were as follows (Table 1). Laboratory findings were serum protein 7.2 g/dL (normal level: 5.8-8.0 g/dL), albumin 4.3 g/dL (normal level: 3.1-5.2 g/dL), sodium 139 mEq/L (normal level: 135-145 mEq/L), potassium 4.4 mEq/L (normal level: 3.5-5 mEq/L) and random urine analysis showed blood 2+, protein 2+, protein 380 mg/dL, randome urine protein to creatinine ratio 3.7. On renal biopsy, his diagnosis was confirmed as Henoch-Schönlein purpura nephritis, ISKDC grade III.

Two days after renal biopsy, intravenous methylprednisolone pulse therapy (IMPT) of 0.5 g/day was begun for three consecutive days. Subsequently oral prednisolone (Calcort) 2 mg/kg and oral cyclophospamide 2 mg/kg were administered. After discharge, he was followed up every week taking medicines. And, blood pressure, CBC, BUN, serum creatinine, serum albumin, serum electrolytes, urinalysis, and random urine protein to creatinine ratio were monitored weekly while 24-hour urine collection for protein and electrolytes was done intermittently. His nocturia had begun right after IMPT, which was once to several times per night, and persisted for 2 months. During 2 months after IMPT, potassium level ranged between 3.0-3.6 mEq/L and 24-hour urine volume between 1.6-2.2 liter/day and urine potassium between 46-54 mEq/day. His blood pressure was maintained normotensive. His one-day voiding diary showed voiding volume of 70-200 mL, urine volume of 1,800 ml/day, 11 times of voiding frequency, and none of dysuria, urgency, incontinence, hesitancy, polydypsia and caffeinated drink. After he took potassium chloride (K-contin, K^+ 24 mEq/day), his potassium level returned to 4.2 mEq/L, 24-hour urine volume decreased to 900 ml/day. And thereafter his nocturia had been disappeared. Other laboratory findings were Mg 2.23 mg/dL (normal level: 1.4-2.4 mg/dL), plasma renin acitivity (PRA) 43.7 ng/mL/hr (normal level: 1.31-3.95 ng/mL/hr), aldosterone 10.2 ng/dL (normal level: supine 1-16 ng/dL, standing 4-31 ng/dL), ACTH 2.0 pg/mL (normal level: AM 8-10hr 10-60 pg/mL, PM 8-10hr 6-30 pg/mL), ADH 0.19 pg/mL (normal level: 0-4.7 pg/mL), TSH 0.69 uIU/mL (normal level: 0.35-5.5 uIU/mL), FT4 1.26 ng/dL (normal level: 0.89-1.76 ng/dL), urine cortisol 0.21 ug/day (normal level: 28.5-213.7 ug/day), urine Osm 845 mOsm/kg (normal level: 390-1,090

mOsm/kg), urine S.G 1.020, and transtubular potassium gradient (TTKG) 3.5.

Discussion

There are few reports on development of polyuria after IMPT. But, it has already been known that IMPT can cause hypokalemia from urinary potassium wasting [7] and that hypokalemia per se can induce mild polyuria as well [8].

A normal subject can, in the presence of potassium depletion, lower urinary potassium excretion below 25 to 30 meq per day; values

Table 1. A Flow Chart of Laboratory Findings

Hospital day	-6*	HD#1†	HD#4	+9‡	+31	+52	+59	+115
			IMPT#2§					2
Protein (g/dL)	7.2			6.1	5.6	5.5	6.0	6.2
Albumin (g/dL)	4.3			3.8	3.8	3.5	3.8	3.9
BUN (mg/dL)	9.4			8.6	10.6	8.7	13.1	8.4
Cr (mg/dL)	0.7			0.6	0.6	0.7	0.6	0.7
Ca (mg/dL)	8.9			7.6	7.6	7.8	8.1	9.0
P (mg/dL)	4.7			4.0	3.6	3.5	4.6	5.1
AST (mg/dL)	24			16	17	16	15	18
ALT (mg/dL)	11			14	15	20	19	14
Na (mEq/L)	139			139	140	141	139	140
K (mEq/L)	4.4			3.4	3.6	3.0	4.2	4.2
Cl (mEq/L)	101			101	103	107	107	107
TCO2 (mg/dL)	29.3			26.8	34.0	26.6	24.0	24.0
Osm (S) (mOsm/kg)	290						296	298
FeNa (%)					1	1	1.1	0.04
Urine S.G	>=1.030	1.020	1.015	1.025	1.025	1.010	1.020	1.020
Protein	2+	3+	2+	3+	3+	2+	2+	3+
RBC	5-9	5-9	10-30	3+	10-30	5-9	5-9	10-30
Na (mEq/L)			55				213	
K (mEq/L)			32				41.4	
Cl (mEq/L)			55				165	
Osm (U) (mOsm/kg)			299				845	745
24 hour urine								
Total Volume (mL)		1,100	2,200			1,940	1,600	900
Protein (mg/day)		1,702.8	3,174.6			2797.48	1,521.6	280.8
Na (mEq/day)		103.4			213	176.5	97.6	36.9
K (mEq/day)		16.5			41.4	52.13	46.24	35.01
Cl (mEq/day)		92.4			165	207.5	145.6	49.5
Microalbumin (mg/day)		1,441				1703	1,035.2	261.9

*Date of following up out patient departments before admission date
†Hospital day
‡Date of following up out patient departments from discharge date
§Second day of high dose methylpredisolone pulse therapy
Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; Osm (S), serum osmolarity; Urine S.G, urine specific gravity; Osm(U), urine osmolarity; Cr(U), urine creatinine

above this level reflect at least a contribution from urinary potassium wasting [9]. However, potassium wasting may be minimized or even masked if sodium and water delivery to the distal potassium secretory site is minimized by underlying volume depletion [10]. Thus, urinary sodium excretion should be above 30 to 40 meq per day to avoid this problem [11]. In this case with mild hypokalemia (<3.5 mEq/L), keeping urine potassium level of more than 30 mEq/day for several weeks without volume depletion (urine sodium >40 mEq/L), means that his hypokalemia was due to urinary potassium wasting, and we think that was probably caused by IMPT because there was no other cause of renal potassium loss. Although cyclophosphamide can be a causative agent of hypokalemia in this case, we think that is highly unlikely because the characteristics of renal toxicity associated with cyclophosphamide are proximal tubular wasting of glucose, phosphate, bicarbonate, sodium, potassium, and amino acids and hypomagnesemia, and decreased glomerular filtration rate [12]. And the fact that his nocturia developed from the third day after IMPT the day before cyclophosphamide treatment supports our belief favorably. Furthermore, our review of the medical literature did not identify any possible casual relation between cyclophophamide therapy and hypokalemia induced polyuria.

The causes of hypokalemia due to increased urinary losses are as follows: use of diuretics, primary mineralocorticoid excess, loss of gastric secretions, distal flow of nonreabsorbable anions, metabolic acidosis, hypomagnesemia, use of amphotericin B, salt-wasting nephropathies like Bartter and Gitelman syndrome, and polyuria [11]. Drugs with mineralocorticoid or glucocorticoid effects, such as prednisone and hydrocortisone, can cause hypokalemia because they increase potassium excretion nonspecifically through their effect on the filtration rate and distal sodium delivery [20]. If polyuria per se induces hypokalemia as in primary polydipsia and central diabetes insipidus, urine output must be over 5 to 10 liter/day x body surface area (BSA/m^2) in children [11]. In this case, excessive corticosteroids by administering high dose of methylprednisolone seemed to induce increased urinary potassium losses leading to mild hypokalemia. Tamez-Pérez et al. [13] reported that the prevalence of mild hypokalemia in 110 patients with IMPT (1 g/day for three consecutive days) was 17.27 % and no cases of severe hypokalemia occurred.

The development of mild polyuria, averaging 2 to 3 liters per day is one of complications of hypokalemia [8]. The polyuria is related to both increased thirst and mild nephrogenic diabetes insipidus. Increased thirst is associated with increased central nervous system levels of angiotensin II, a hormone that, besides its other effects, regulates thirst. Hypokalemia also impairs the kidney's ability to concentrate the urine maximally [8]. This appears to occur because hypokalemia causes defective activation of renal adenylate cyclase, preventing antidiuretic hormone-stimulated urinary concentration [14]. Several other mechanisms of K^+ deprivation-induced polyuria have been proposed to explain the defect in urinary concentrating ability in K^+ depletion, including prosta-

glandin overproduction [15], primary polydipsia [16], altered ADH release by the posterior pituitary gland [17], abnormal medullary oxidative metabolism [18], and reduced medullary solute [19].

For the first time, we experienced the development of polyuria and noctuira after IMPT. So, we could not prevent patient's distress arising from frequent nocturia until the patient complained of it for himself. In the future, after IMPT, not only detailed history taking of nocturia, but also monitoring of urine volume as well as serum and urine potassium level at regular follow-up is considered necessary because even mild hypokalemia can provoke urinary concentration defect.

한 글 요 약

Henoch-Schönlein Purpura 신염 환자에서 경정맥 고용량 스테로이드 충격요법 후 발생된 저칼륨혈증으로 인한 다뇨증과 야간뇨

차의과대학교 분당차병원 소아청소년과

김 근 정 · 이 준 호

경정맥 고용량 스테로이드 충격요법(IMPT)의 부작용으로는 고혈압, 동성 서맥, 심방심실 전도장애, 심방 세동, 심방 조동, 심실 빈맥 등의 부정맥, 구토, 구역질 등의 소화기 장애, 백내장, 저칼륨혈증, 그리고 감염성 질환 등이 있다. 그 중, 저칼륨혈증은 IMPT를 받는 환자의 17% 정도에서 경미하게 나타날 수 있다. 저칼륨혈증이 신수질의 요농축 능력을 저하시켜 다뇨가 발생할 수 있다는 사실은 이미 알려져 있지만, IMPT후 경미한 저칼륨혈증으로 인해 심한 야간뇨과 다뇨증이 발생하였다는 보고는 별로 없다. 이에 본 저자들은 다량의 단백뇨와 혈뇨를 보이는 HSP 신염환자에게 세 차례의 IMPT 시행 후 환아에게 발생한 경미한 저칼륨혈증으로 인한 심한 야간뇨와 다뇨증의 발생을 경험하였기에 이에 보고하는 바이다.

References

1) Joseph TF, Willam ES, Timothy EB, David BK, Aileen BS. Treatment of Henoch-Schönlein purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. Am J Nephrol 2001;21:128-33.
2) Jonathan DA, Brian MF, Gil JG, Gross ED. Sinus bradycardia after intravenous methylpredisolone. Pediatrics 2007;119:e778-82.
3) Abraham C, Richard T, Richard D. Prednisolone in the treatment of rheumatoid arthritis. N Engl J Med 1955;253:1150-2.
4) Andreas HB. Steroid-resistant kidney transplant rejection: Diagnosis and treatment. J Am Soc Nephrol 2001;12:48-52.
5) Pankaj H, Rajendra NS. Pulse corticosteroid therapy with methylprednisolone or dexamethsone. Indian journal of pediatrics 1998;65:557-60.
6) Patric N, Renée H. Methylprednisolone pulse therapy in the treatment of severe forms Schönlein-Henoch purpura nephritis. Pediatr Nephrol 1998;12:238-43.
7) Bonnotte B, Chauffert B, Martin F, Lorcerie B. Side-effects of high-dose intravenous (pulse) methylprednisolone therapy cured by potassium infusion. Br J Rheumatol 1998;37(suppl 1):109.
8) Mujais SK, Katz AI. Potassium deficiency. In : Seldin DW, Giebisch G, editors. The kidney: Physiology and Pathophysiology. New York : Raven Press Ltd, 1992:2249-78.
9) Squires RD, Huth EJ. Experimental potassium depletion in normal human subjects. I. Relation of ionic intakes to the renal conservation of potassium. J Clin Invest 1959;38:1134-48.

10) Young DB. Quantitative analysis of aldosterone's role in potassium regulation. AM J Physiol 1988;255:811-22.
11) URL://http://www.uptodate.com/home/index.html
12) Jones DP, Chesney RW. Renal toxicity of cancer chemotherapeutic agents in children: ifosfamide and cisplatin. Curr Opin Pediatr 1995;7:208-13.
13) Tamez-Pérez HE, Cisneros-Pérez V, Cedillo-Rodríguez JA, Diaz-De-León-González E, Torres-Valenzueia M, Tamez-Peña AL et al. Prevalence of hypokalemia in patients with methylprednisolone pulse therapy. Rev Invest Clin 2009;61:194—7.
14) Kim JK, Summer SN, Berl T. The cyclic AMP system in the inner medullary collecting duct of the potassium-depleted rat. Kidney Int 1984;26:384—91.
15) Galvez OG, Bay WH, Roberts BW, Ferris TF. The hemodynamic effect of potassium d-eficiency in the dog. Circ Res 1977;40 (suppl 1):11-6.
16) Terris J, Ecelbarger CA, Marples D, Knepper MA, Nielsen S. Distribution of aquaporin-4 water channel expression withing rat kidney. Am J Physiol Renal Physiol 1995; 269:F775-85.
17) Rutecki GW, Cox JW, Robertson GW, Francisco LL, Ferris TF. Urinary concentrating ability and antidiuretic hormone responsiveness in the potassium-depleted dog. J Lab Clin Med 1982;100:53-60.
18) Kannegiesser H, Lee JB. Role of outer medullary metabolism in the concentrating defect of K+ depletion. Am J Physiol 1971; 220:1701-7.
19) Manitius A, Levitin H, Beck D, Epstein FH. On the mechanism of impairment of renal concentrating ability in potassium defiency. J Clin Invest 1960;39:684-94.
20) Gennari FJ. Hypokalemia. N Engl J Med 1998;339:451-8.