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Single Case – General Neurology

Posterior Reversible Encephalopathy Syndrome Induced by Hypomagnesemia due to *Clostridium Difficile* in a Patient with Kidney Transplant

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Keywords
Hypomagnesemia · Posterior reversible encephalopathy syndrome · Hypoparathyroidism · *Clostridium difficile*

Abstract
Hypomagnesemia is found in 12% of hospitalized patients and up to 60% of intensive care unit patients and is associated with a variety of organ dysfunction. Posterior reversible encephalopathy syndrome is a neurologic hyperperfusion disorder that mostly affects posterior portions of the brain. Various theories were proposed to explain whether hypomagnesemia is etiology or associated with posterior reversible encephalopathy syndrome (PRES). A patient with kidney transplantation suffered from fatigue and reduced urine output due to chronic diarrhea induced by *Clostridium difficile*. Hypoparathyroidism in addition to persistent hypocalcemia and hypokalemia was observed and suggested magnesium depletion with normal serum levels. Thereafter, the status was complicated with delirium, seizures, and coma. Neurological status rapidly improved after adding intravenous magnesium sulfate to antiepileptic drugs. The second magnetic resonance imaging (MRI) showed vasogenic edema compatible with posterior reversible encephalopathy syndrome. Therefore, magnesium depletion, with normal serum levels, was considered the most implicated etiology of the syndrome in this patient. Also, hypomagnesemia during the acute phase of the syndrome and excluding all other etiology support this theory. Our case highlights hypomagnesemia-induced PRES, despite the normal serum level. Serum magnesium dropped during the acute phase of PRES, and magnesium should be maintained at the high normal limit, regardless of

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normal serum level. MRI findings might present after few days of symptoms; this might delay appropriate treatment.

Introduction

Magnesium plays an essential role in numerous cellular processes such as regulation of ion channels, enzyme activities, and stabilization of membrane structures. Hypomagnesemia is found in 12% of hospitalized patients, and up to 60% of intensive care unit (ICU) patients may be asymptomatic or associated with a variety of organ dysfunctions (cardiovascular, central nervous system, etc.) [1]. Posterior reversible encephalopathy syndrome (PRES) is a neurologic hyperperfusion disorder resulting from increased cerebral blood flow, capillary leakage, and edema. The predilection to affect posterior portions may be due to a lower threshold for autoregulation in posterior circulation of the brain. PRES occurs in the context of disorders such as eclampsia, chemotherapy, immunosuppressive drugs, hypertensive encephalopathy, and renal failure [2]. Various theories were placed to explain whether hypomagnesemia is etiology or associated with PRES. This case presents hypomagnesemia due to chronic *Clostridium difficile* (*C. difficile*) diarrhea in a patient with kidney transplant, thereafter complicated with hypoparathyroidism and PRES, which rapidly improved after magnesium correction.

Case Presentation

A 30-year-old woman was admitted to the Nephrology Department of Al Assad University Hospital due to chronic diarrhea 3 months ago, fatigue, and reduced urine output. Her medical history included kidney transplantation for end-stage renal disease 10 years earlier and hypertension (HTN). Her medications were tacrolimus, mycophenolate mofetil, prednisone, ramipril, amlodipine, hydrochlorothiazide, esomeprazole, alfa calcitriol, and epoetin alfa. She took intermittent courses of metronidazole with frequent recurrences. On physical examination, the patient showed exhaustion with dyspnea on rest, blood pressure (BP) 100/60 mm Hg, respiratory rate 28/min, pulse 94/min, oxygen saturation 96%, urinary output 700 mL/24 h, and positive Trousseau sign. Laboratory findings on admission are given in Table 1. Her basal creatinine (Cr) – before diarrhea – was 2.4 mg/dL. To determine the cause of chronic diarrhea, additional tests were performed: anti-CMV-IgG (539, high), anti-CMV-IgM (0.3, negative), CMV-PCR negative, anti-tissue transglutaminase (5.8, up to 10), total IgA (43.6, normal range 70–400), and toxins of *C. difficile* (toxins A and B) were positive. We started treatment with oral vancomycin along with adequate fluids and electrolyte replacement for potassium (K), calcium (Ca) and sodium bicarbonate. The clinical status was improved, acidemia gradually disappeared, and serum Cr (S-Cr) returned to the basal level. In the next 2 days, hypokalemia and hypocalcemia persisted, despite empirical magnesium (Mg) replacement on admission with serum Mg (S-Mg; 2.1 mg/dL, range 1.7–2.3). Hypoparathyroidism (parathyroid hormone = 29 pg/mL) was observed (desired range in CKD stage 4 is 70–120 pg/mL) [1], and alfa calcitriol was stopped. Frequent replacement of electrolytes (Ca, K, Mg) was carried out, and serial serum levels are given in Table 2. On day 9 (March 11, 2021), the patient had a headache. On day 11 (March 13, 2021), she had delirium and agitation and refused her daily medications, which caused BP elevation (Table 2). Magnetic resonance imaging (MRI),

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Table 1. Laboratories on admission

WBC	11.7	Na	135	ESR	19
HB	12.1	K	2.7	PH	7.11
HT	37	Cl	104	PCO2	14
PLT	263	Ca	5.6	PO2	146
Ur	179	Ca Corrected	6	HCO3	4.6
Cr	4.8	P	7.9	SO2%	98
GLU	88	CRP	0.1	AG	26
TP	4.7	UA	9.6	ΔΔ	0.8
ALB	3.5	CrCl	12	Tacrolimus trough	4.6 (5–20)
AST	18	ALT	16	PTH	29

WBC, white blood count; HB, hemoglobin; HT, hematocrit; PLT, platelet; Ur, urea; Cr, creatinine; GLU, glucose; TP, total protein; ALB, albumin; AST, aspartate transaminase; ALT, alanine aminotransferase; Na, sodium; K, potassium; Ca, calcium; P, phosphorus; CRP, C-reactive protein; UA, uric acid; CrCl, Cr clearance; ESR, erythrocyte sedimentation rate; AG, anion gap; PTH, parathyroid hormone.

Table 2. Electrolytes and BP monitoring during admission

Date	Ca mg/dL	K mg/dL	Mg mg/dL	ALB mg/dL	Cr mg/dL	BP	Mg sulfate supplement, g
Admission Mar 4, 2021	5.6	2.7	–	3.5	4.8	100/60	2.5
Mar 5, 2021	7.2	2.9	2.1	2	4.9	115/70	–
Mar 7, 2021	5.7	2.6	–	3	3.8	120/80	2.5
Mar 10, 2021	6.7	4.6	–	2.9	2.7	130/80	5
Mar 12, 2021	7	3.4	–	3.5	2.8	150/100	–
Mar 13, 2021	7.9	3.4	–	3.4	2.8	150/90	–
Mar 14, 2021	7.2	3.2	–	3.3	2.5	145/90	–
Mar 16, 2021	6.6	3.3	1.7	3.3	2.2	160/100	2.5
Mar 18, 2021 ICU	8.1	4.7	1.4	3.3	3.5	150–180/ 100–120	5
Mar 20, 2021	7.8	3.8	–	–	3.1	150/100	Mg PO
Mar 22, 2021	7.4	3.7	2.1	2.5	2.1	140/95	Mg PO
Mar 25, 2021 Discharge	8.4	3.8	–	3.2	2.7	130/75	Mg PO

Mg, magnesium; po, per os; BP, blood pressure; Cr, creatinine; ICU, intensive care unit.

cerebrospinal fluid, and serologic tests were normal. A psychiatric consult was performed and prescribed haloperidol. On day 16 (March 18, 2021), the patient developed seizures and coma, with a Glasgow Coma Scale (GCS) score of 6 and was transmitted to the ICU. In the ICU, the patient was intubated and received phenytoin without improvement; thereafter, valproate and IV magnesium sulfate were added because of low S-Mg (1.4 mg/dL). The neurological status was rapidly improved, and she returned consciously (GCS = 15) in the same day. Panel tests for viral infections on cerebrospinal fluid came back negative (Table 3). On day 20 (March 22, 2021), MRI was repeated which showed vasogenic edema compatible with PRES (Fig. 1).

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Table 3. Detection of viral infection in CSF

COVID-19 (IgG-IgM)	Negative	HHV 7	Negative
HSV I	Negative	Human papilloma virus (parvovirus 19)	Negative
HSV II	Negative	Human adenovirus virus	Negative
VZV	Negative	CMV	Negative
HPV	Negative	EBV	Negative
HHV6	Negative	Enterovirus	Negative

HHV, human herpes virus; HPV, human papilloma virus; VZV, varicella zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HSV, herpes simplex virus; CSF, cerebrospinal fluid.

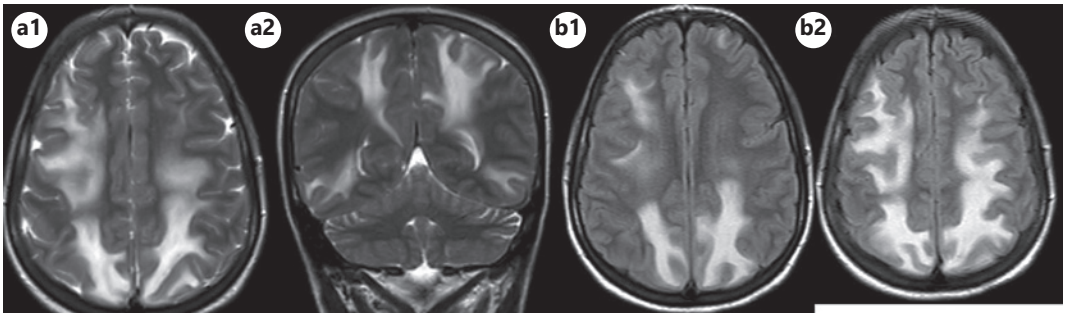

Fig. 1. MRI shows bilateral subcortical white matter lesions in parietal, occipital, and temporal lobes. Hyperintense on T2-weighted (**a1–2**). Hyperintense on FLAIR (**b1–2**). MRI, magnetic resonance imaging.

The patient still suffered from blurred vision, headache, and weakness after ICU discharge. Few days of observation, the patient was discharged; however, she had COVID-19 infection after 2 weeks and died later.

Discussion

This report presented a kidney transplant patient with PRES and hypoparathyroidism due to hypomagnesemia, which induced by chronic *C. difficile* diarrhea; moreover, the patient's status rapidly improved with magnesium supplementation. HTN, up to a hypertensive emergency, has been reported in a majority of PRES patients. About 30% of patients have been shown normal or slightly elevated BP [3]. The patient in this report had slightly BP elevated after being delirious but developed emergent HTN in the ICU. This mad HTN likely occurred as a consequence of primary endothelial dysfunction, rather than a cause of PRES. Furthermore, Mg correction was associated with rapid improvement of the neurologic status and HTN; this made hypomagnesemia most likely the cause of PRES. Magnesium (Mg) is the second most intracellular cation, and approximately 1% is extracellular. Therefore, the serum Mg (S-Mg) level is not reliable for total body depletion. Persistent hypocalcemia and/or hypokalemia, which is refractory to supplementation, is considered a clue to diagnose true Mg depletion [1]. This is observed in this patient, who had Mg depletion with normal S-Mg, which is called normomagnesemic magnesium depletion. Hypomagnesemia was described in the context of PRES; however, the definite correlation still in doubt. Most cases described low Mg as concomitant or contributor to PRES [4–6], but a few cases ascribed as a cause [7–9]. In a retrospective study of 19 patients, hypomagnesemia

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was consistently observed during the acute phase of PRES, regardless of different etiologies; however, the mean S-Mg was normal before neurological disorder [5]. In the current case, magnesium depletion was noticed, and S-Mg dropped during the acute phase (1.4 mg/dL). One report was reviewed with 11 cases of hypomagnesemia with cerebellar syndromes, and 6 patient had diarrhea due to short bowel syndrome [8]. However, neurologic disorders induced by hypomagnesemia due to *C. difficile* diarrhea have not been reported. Hypocalcemia often occurs with severe Mg depletion (usually <1.2 mg/dL), which is due to decreased secretion or resistance to parathyroid hormone [1]. However, S-Mg was normal in our patient, hypoparathyroidism and hypocalcemia had occurred. MRI is the most important diagnostic tool, which shows bilateral distribution, especially in parieto-occipital lobes with hyperintense T2-weighted and FLAIR sequences [3]. In this patient, radiological findings were presented after 6 days of symptoms; this might delay appropriate treatment. Our case highlights hypomagnesemia-induced PRES, despite normal serum levels, and rapid improvement after magnesium supplementation.

Conclusion

Magnesium depletion should be suspected in all patients with PRES. Serum magnesium dropped during the acute phase of PRES. MRI findings might present after few days of symptoms; this might delay appropriate treatment. Therefore, magnesium should be maintained in the high-normal limit, regardless of the normal serum level. Magnesium supplementation might be beneficial due to its effects as an anticonvulsive agent and vascular endothelium stabilization.

Statement of Ethics

Written informed consent was obtained from the husband of the patient for publication of this case report and any accompanying images, and he has provided a copy of the consent form. The article is exempt from ethical approval of Damascus University Research Center because it is not an experimental trial.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Mohammad Alsultan wrote the manuscript, searched the literature, and submitted the article. Prof. Qussai Hassan made article corrections, literature search, and supervised the case.

Data Availability Statement

The data that support the findings of this study cannot be shared due to containing information that could compromise the privacy of the patient. Queries regarding the data in this article should be addressed to Dr. Mohammad Alsultan.

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