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CASE REPORT / *OLGU SUNUMU*

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Hypermagnesemia Induced Paralytic Ileus: A Case with Normal Renal Function and Review of the Literature

Hipermagnezemi İlişkili Paralitik Ileus: Normal Renal Fonksiyonlu Bir Olgu ve Literatür Değerlendirmesi

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ABSTRACT Hypermagnesemia is considered to be rare and usually iatrogenic; occurring, for example, after intravenous Mg administration, oral ingestion of Mg-containing antacids or cathartics. We describe such a patient who developed severe hypermagnesemia after ingestion of unknown amount of Mg-containing oral laxatives, Sodium Phosphate and Aluminum hydroxide. A 79 year-old woman was admitted to our hospital's emergency department history of constipation and abdominal pain and vomiting. She received unknown amount magnesium (Mg) Hydroxide and Lactulose. The laboratory work-up on admission to emergency department showed magnesium 9.37 mg/dL. Abdominal X-ray showed multiple air-fluid levels concerning for small bowel obstruction (Figure 1), confirmed with abdominal computed tomography (Figure 2). She was admitted to general surgery department at the same day. The next morning she was found to be lethargic and did not respond well to verbal and painful stimuli. Then she was transferred to intensive care unit (ICU). On admission to the ICU, she was unconscious. Bowel sounds was not audible. She was immediately intubated and connected mechanical ventilation because of respiratory depression. Intravenous liquid, diuretic and calsium infusion was used. At fourth day patient has conscious and was extubated and followed by nasal oxygen therapy. Mg level was gradually decreased to 2.5 mg/dL at fourth day. Bowel sounds were audible first. At fifth day flatus expelled first time. At seventh day patient defecated first time and at seventh day oral regim 1 was started. At eight day patient transferred to general surgery service.
Mg is the fourth most abundant cation in the human body. Mg homeostasis is dependent mainly on gastrointestinal absorption and renal excretion. Massive oral Mg ingestion may result in hypermagnesemia if the absorbed amount of Mg exceeds the renal excretion capacity. Hipermagnesemia can cause ileus. Hypermagnesemia should be considered in patients, particularly in elderly presenting with ileus.
Keywords: Hypermagnesemia, ileus, normal renal function, respiratory depression

ÖZ Hipermagnezemi nadir görülür, genelde intravenöz magnezyum verilmesi, magnezyum (Mg) içeren antiasit ve katartiklerin oral uygulaması, Mg içeren preparatların prosedürlere bağlı retroperitoneal veya peritoneal kaçakları sonucu ortaya çıkar. Bu olgu sunumumuzda kabızlık şikayeti sonrası bilinmeyen miktarda Mg içeren laksatif alımı sonrası oluşan ciddi hipermagnezemi sonucu ortaya çıkan paralitik ileus olgusunu sunmak istiyoruz.
Bir haftadır konstipasyon, karın ağrısı, kusma şikayetleri olan 79 yaşında kadın hasta acil servise getirilmiş. Hasta bilinmeyen miktarda Magnesie Calcinee ve Laktuloz ve B.T enema kullanmış. Acil servisdeki laboratuvar çalışmasında Mg: 9,37 mg/dL olarak bulunmuş. Abdominal direkt grafide ince barsak tıkanıklığını gösteren hava sıvı seviyeleri tespit edilmiş (Şekil 1), abdominal tomografi ile bu bulgular onaylanmış (Şekil 2,3). Hasta aynı gün İleus tanısı ile genel cerrahi servisine yatırılmış ve nazogastrik drenaja alınarak takibe başlanmış. Ertesi sabah hasta letarjik hale gelmesi ve sözlü ve ağrılı uyaranlara cevap vermemesi üzerine dahili yoğun bakım ünitesine (YBÜ) yatırıldı. Dahili YBÜ'de GKS: 5, bilinç kapalı ve solunumun yüzeyel olması sebebiyle entübe edilen hasta ventilatöre bağlandı. Batın muayenesinde barsak sesleri alınamıyordu. Takip sırasında intravenöz sıvı, diüretik tedavisi ve kalsiyum infüzyonu uygulandı. Hastanın takibinde batın distansiyonu azaldı, YBÜ yatışının 4. gününde bilinci açıldı ve ekstübe edildi, başlangıçta alınamayan barsak sesleri alınmaya başlandı. Hastanın YBÜ yatışının 4. gününde Mg düzeyi 2,55 mg/dL'ye geriledi. Ekstübasyon sonrası hasta nazal O_2 ile izlendi. YBÜ yatışının 5. gününde gaz-gaita çıkışı başlayan hastaya, 7. gün oral beslenme başlandı ve 8. gün genel cerrahi servisine transfer edildi. Mg vücutta en fazla bulunan katyonlar

arasında dördüncü sırada gelmektedir. Mg dengesi gastrointestinal sistem ve böbreklere bağlıdır. Ancak temel organ böbreklerdir. Normalde 1/3 oranında emilmektedir. Bağırsak pasajının bozulduğu durumlarda oral alınan Mg içerikli laksatifler yüksek miktarlarda emilerek kan Mg düzeyini aşırı yükseltebilir ve bu durum ileus'la sonuçlanabilir. Doktorların özellikle yaşlı hastalarda böbrek fonksiyonları normal olsa bile bu durumu göz önünde bulundurması gereklidir.
Anahtar Kelimeler: Hipermagnezemi, ileus, normal böbrek fonksiyonu, solunum depresyonu

Introduction

Well-established causes of paralytic ileus include electrolyte disturbances (commonly hypokalemia), pancreatitis, and medications including narcotics and anticholinergics (1). Hypermagnesemia is considered to be rare and usually iatrogenic; occurring, for example, after intravenous magnesium (Mg) administration, oral ingestion of Mg-containing antacids or cathartics, or procedure-related retroperitoneal or peritoneal leakage of Mg-containing preparations. The kidney is the principal organ involved in Mg regulation, and therefore hypermagnesemia commonly occurs in the presence of renal failure (2). Hypermagnesemia is a rare cause of ileus. We describe such a patient who developed severe hypermagnesemia after ingestion of unknown amount Mg Hydroxide (Magnesie Calcinee which contains 100 gr per bottle) and Lactulose (Duphalac) and Sodium Phosphate (B.T enema which contains Sodium Phosphate monobasic X-hydrate and dibasic X-hydrate) for constipation and Aluminum hydroxide - Mg carbonate combination (Gaviscon Liquid: Aluminum hydroxide 9 5mg - Mg carbonate 358 mg) for peptic ulcer.

Case Report

A 79-year-old woman was admitted to the hospital's emergency department on February 5, 2018, for a week history of constipation and abdominal pain with vomiting. Her past medical history was significant for diabetes mellitus, hypertension, arrhythmia, dementia, and previous operation history for peptic ulcer perforation and ileus (9 years ago). She has recently received unknown amount Mg Hydroxide and Lactulose and Sodium Phosphate for constipation and Aluminum hydroxide - Mg carbonate combination for peptic ulcer. The laboratory work-up on admission showed normal complete blood count, mild renal injury with creatinine 1.2 mg/dL, potassium 2.7 mEq/L, normal hepatic function, Mg 9.37 mg/dL, calcium 9.2 mg/dL. Abdominal X-ray showed multiple air-fluid levels concerning for small bowel obstruction (SBO; Figure 1), confirmed with abdominal computed tomography (CT) that showed partial SBO with transition point in the right lower quadrant and collapsed distal ileum (Figure 2). She was then admitted to general surgery department on the same day and was monitored with nasogastric tube (NG) decompression. The next morning she was found to be lethargic and unresponsive to verbal and painful stimuli and was transferred to medical intensive care unit (ICU).

On admission to the ICU, she was unconscious and Glasgow Coma scale score was 5. Her temperature was 36.2 ºC, with a blood pressure of 133/54 mmHg and pulse rate of 70/min under noradrenaline administration, ECG was normal. Respiration rate was 32/min. No heart murmur, crackles or rubs were audible from her chest. Her abdomen was distended and bowel sounds were not audible. Results of the laboratory examinations were as follows: potassium, 3.0 mEq/dL; chloride, 88 mEq/dL; Mg, >9.50 (Table 1, 2, 3); phosphate, 3.8 mg/dL; blood urea nitrogen,146 mg/dL; creatinine, 0.93 mg/dL; calcium, 7.1 mg/dL; albumin,3.1 g/dL; and C-reactive protein, 3.35 mg/dL; creatinine phosphokinase 225 U/L. The findings of the initial arterial blood gas analysis under 4 liters/min nasal oxygen showed respiratory acidosis (pH, 7.22; $PaCO_2$, 95.9 mmHg; PaO_2, 106 mmHg; and bicarbonate, 32 mEq/dL). Infusion of normal saline, furosemide and potassium replacement were started.

After transfer to ICU, she was immediately intubated and mechanically ventilated because of unconsciousness and respiratory depression. She was ventilated under

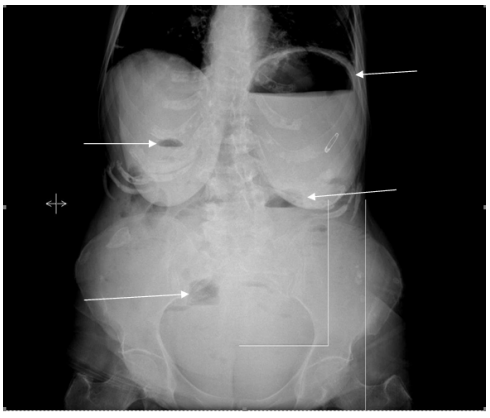

Figure 1. X-Ray of abdomen on admission to emergency department (air liquid levels)

Table 1. Patient's electrolyte status and clinical course according to days					
	Sodium	**Potassium**	**CO_2**	**Magnesium**	**Symptoms**
Normal	134-146 mEq/L	3.5-5.2 mEq/L	32-48 mmHg	1.6-2.6 mg/dL	-
ED	128	2.7	73	9.37	Ileus no bowel sounds
Day 1*	138	3	95	>9.50	Ileus no bowel sounds
Day 2*	148	3	26.9	7.89	Decreased distention
Day 3*	153	3.2	48	4.79	Minimal distention, fever
Day 4*	156	3.5	41	2.55	Bowel sounds
Day 5*	151	3.6	38.7	2.12	Flatus: + +
Day 6*	146	3.2	33.6	1.66	Flatus: + +
Day 7*	140	3.8	33.8	1.71	Defecation, oral regime1
Day 8*	144	3.9	33.2	1.66	Discharged from ICU

*: In ICU, ED: Emergency department, ICU: Intensive care unit

Table 2. Effects of hypermagnesemia in relation to serum magnesium levels*		
Serum Mg level		**Mg levels related manifestations**
mg/dL	**mEq/L**	
1.7–2.4	1.4–2.1	Normal serum level
5–8	4–7	Serum levels during parenteral treatment, nausea, vomiting, cutaneous flushing, bradycardia, hypotension
9–12	8–10	Absent deep tendon reflexes, somnolence
>15	>12	Respiratory paralysis, depression, complete heart block
>20	>16	Cardiac arrest in asystole

*: Adopted from references 1 and 7, Mg: Magnesium

Table 3. Cases of hypermagnesemia-induced paralytic ileus and perforation (literature search from english-language journals)*						
References	**Sex/Age (yrs)**	**Serum Mg (mg/dL)**	**Serum Cr (mg/dL)**	**Cause of hypermagnesemia**	**Clinical manifestations**	**Outcome**
Kontani et al. (1)	F/76	16.6	1.4	Magnesium citrate (laxative)	Hypotension, lethargy, tachycardia, atrioventricular block	Ileus, recovered
Golzarian et al. (3)	F/65	5.1	1.0	Magnesium citrate (laxative)	None	Ileus, recovered
	F/67	8.1	2.6	Magnesium sulfate (Epsom salt)	None	Ileus, recovered
Onishi and Yoshino (5)	M/89	12.6	1.5	Magnesium citrate (laxative)	Hypotension, lethargy	Intestinal perforation, died
Kutsal et al. (8)	F/14	14.9	0.47	Magnesium hydroxide (laxative)	Hypotension, lethargy, diminished DTR, bradycardia, respiratory arrest	Ileus, recovered

Mg: Magnesium; Cr: Creatinine; M: male; F: Female; DTR: Deep tendon reflex, *: Adopted from references 4

50% oxygen with synchronized intermittent mandatory ventilation volume control mode on mechanical ventilation. Immediate radial arterial catheterization and femoral venous catheterization was performed. A NG was inserted and it was seen that the decompression material was fecal content. On day 2, there was regression of abdominal distention however no defecation was observed. On day 3 the patient's tracheal aspiration culture and urine culture was positive for Escherichia coli growth and meropenem was started as antibiotherapy.

On day 4, patient was consciousness and extubated after successful spontaneous breathing trial. She then followed with 4 liters/min nasal oxygen with oxygen saturation of 98%. Bowel sounds were audible for first time and patient had a control abdominal CT with contrast (urea: 88mg/dL, creatinine: 0.72mg/dL, Figure 3, Figure 4). There was visible decrease in stomach diameter and the bowel dilatation was less significant.

On day 5, flatus expelled first time and on day 7 patient defecated. After that, the next day she was initiated oral diet. On day 8 patient was discharged from ICU to general surgery department.

Discussion

Mg is the fourth most abundant cation in the human body, about half of the total body Mg is in bone, and extracellular Mg accounts for only around 1% (1,2). Approximately one-third of extracellular Mg is protein bound (1,2), while the remaining two-thirds of ionized Mg2+ can diffuse into the kidneys (1). Mg homeostasis is dependent mainly on gastrointestinal absorption and renal excretion, and the kidney is the principal organ involved in Mg regulation (1).

The kidneys are highly effective in regulating body Mg levels (2). Thus, hypermagnesemia is most frequently seen in conjunction with renal insufficiency when patients ingest drugs containing salts of Mg or in patients with small bowel hypomotility disorder (2-5). Even in the presence of abnormal renal function, the body is able to regulate Mg levels by reducing gastrointestinal absorption when serum Mg levels are high (3-5). Therefore symptomatic hypermagnesemia is relatively rare (5).

The toxic effects of Mg become clinically significant at serum levels greater than 2 mmol/liter (4.8 mg/dL) (2,3). The cardiovascular and the neuromuscular systems are most common affected systems (2). Hypermagnesemia is known to cause hypotension, lethargy, atrioventricular block, and respiratory depression by blocking neuromuscular transmission and inhibiting acetylcholine release (3). Initial sign and symptoms of hypermagnesemia include lethargy, confusion, hypotension, and the diminution of deep tendon reflexes due to the neuromuscular blockade effect of Mg (4.8 mg/dL) (2,3). Respiratory depression may be seen at levels >6.5 mmol/L (2,3,6,7).

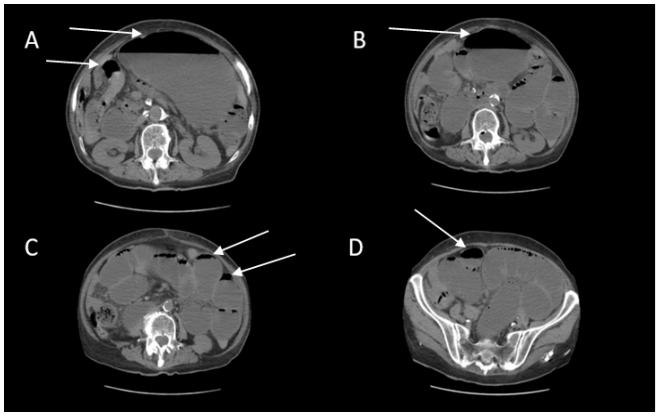

Figure 2. Transverse CT scanning on admission to the emergency department (A-B-C-D, air liquid levels)

CT: Computed tomography

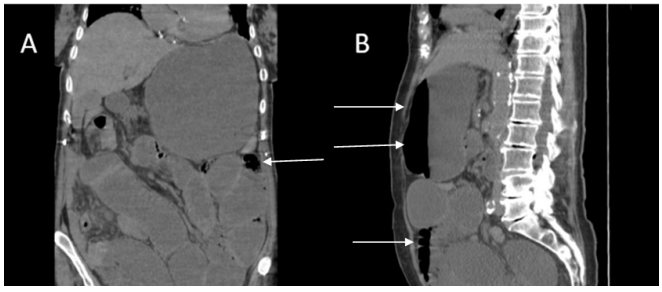

Figure 3. Coronal and Sagittal CT scanning on admission to emergency department (A-B, air liquid levels)

CT: Computed tomography

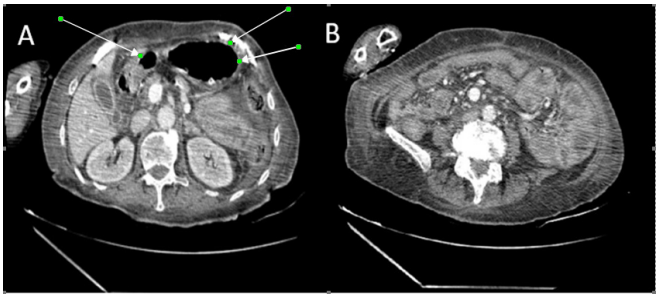

Figure 4. Transverse CT scanning on fourth day after admission to ICU (A-B)

CT: Computed tomography, ICU: Intensive care unit

The gastrointestinal tract (nausea and vomiting) may be affected as well (6). The major gastrointestinal site for Mg absorption is the upper small bowel and its mechanism of regulation is mainly through passive diffusion. Since one-third of orally ingested Mg is absorbed normally, massive oral Mg ingestion may result in hypermagnesemia if the absorbed amount of Mg exceeds the renal excretion capacity (1). Hypermagnesemia can decrease bowel motility by blocking myenteric neurons and interfering with excitation-contraction coupling of smooth muscle cells. In addition, hypermagnesemia can block the peripheral and autonomic nervous system via antagonization of calcium effects, suppression of acetylcholine release, and reduction of postsynaptic membrane responsiveness, and depress the conduction system of the heart and sympathetic ganglia (4).

The paralytic effect of hypermagnesemia on the human intestinal smooth muscle has rarely been suspected clinically (3,4) and has been reported only in a few cases including a patient receiving parenteral Mg sulfate for tocolysis, and in patients on Mg laxatives and Epsom salts for chronic constipation (2). Patient who present with paralytic ileus should have Mg levels checked to rule out a potential cause of paralytic ileus (3). The elderly are at a risk of Mg toxicity as the kidney function declines with age. The age of the subject should be considered while interpreting serum creatinine levels because serum creatinine is not a true indicator of renal function in the elderly subjects. In addition, these subjects are more likely to consume Mg-containing cathartics and antacids (5).

Recommendations for treatment of the patient with hypermagnesemia include: normal saline infusion with diuresis of Mg from the patient's system (3,5), stop other calcium channel blockers as they may act synergistically with Mg (3), infusion of intravenous calcium to treat life threatening cardiac or respiratory compromise, and acute dialysis in the patient with renal insufficiency and continued high levels of Mg (3,5).

In conclusion hypermagnesemia should be considered in patients, particularly in elderly presenting with lethargy, hyporeflexia, paralytic ileus, hypotension, bradycardia, or respiratory depression irrespective of the availability of information regarding the history of Mg ingestion.

Ethics

Informed Consent: The patient informed consent is received verbally.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., K.D., B.Y., Concept: B.Y., Design: A.A., Data Collection or Processing: A.A., Analysis or Interpretation: E.K., Literature Search: S.E., Writing: E.K.

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