CLINICAL VIGNETTE

Critical Hypomagnesemia Exacerbated by Alcohol and Thiazides Presenting with Weakness with a Probable Underlying Genetic Basis

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Case Report

Our patient is a 70-year-old male with coronary artery disease and right coronary artery stenting as well as peripheral arterial disease requiring left superficial femoral artery atherectomy and stent placement. His risk factors include long-term tobacco use, hyperlipidemia, and hypertension. His medications included olmesartan, hydrochlorothiazide, aspirin, clopidogrel, and metoprolol. Since being evaluated by cardiology over a year ago, he has complained of a nearly decade long history of bilateral lower extremity numbness ascribed to a peripheral neuropathy of unknown etiology. He has known degenerative disc disease in the lumbar spine but no history of cervical spinal disease.

His serum magnesium was noted to be 0.9 mg/dL after hospitalization for angina and right coronary artery intervention. He briefly reached 2.4 mg/dL after parenteral magnesium repletion only to fall again to 1.3 mg/dL. He was initiated on 400 mg magnesium oxide replacement, but his level gradually rose to only 1.2 mg/dL. Three weeks after his hospitalization his magnesium was still low at 1.2mg/dL along with his serum sodium which was at 127 meq/L. Hydrochlorothiaizde was stopped and his serum sodium corrected to 135 meq/L, but his magnesium remained at 1.3 mg/dL. He was switched to magnesium plus protein formula initially 133 mg with food three times a day. Even with doubling to 266 mg with food three times a day, the serum magnesium level stayed at 1.3 mg/dL. He then reduced alcohol to two drinks per day and started intravenous magnesium as he was not tolerating high dose oral magnesium and had to reduce back to 133 mg of magnesium with protein with every meal.

The patient's other laboratory results included normal serum phosphorous of 3.3, calcium of 9.7-10 mg/dL, and PTH of 44 pg/mL. Serum potassium was never low despite his low magnesium, ranging between 4.1-4.4 meq/L. Fractional excretion of magnesium is 4.7%, which is diagnostic of magnesium wasting. Of interest the patient's urinary calcium to creatinine ratio was very low (0.006), qualifying as hypocalciuria. His potassium did not rise on amiloride but his serum sodium dropped to 133, which was controlled by increased salt intake and water restriction to <1.5 liters/day.

Figure 1 graphs magnesium and electrolyte trends during admission and parenteral repletion, and the long-term trend after stopping hydrochlorothiazide and increasing magnesium

supplementation. The patient felt some improvement of his symptoms after magnesium supplementation. Low-dose amilioride will be considered if serum magnesium doesn't correct further on maximum oral supplementation.[1]

Discussion

Hypomagnesemia is a relatively common electrolyte disturbance, though it is less investigated since symptoms rarely occur until severely low magnesium levels are reached.[2] Normal serum levels are generally >1.8 milliequivalents/Liter (meq/L), but symptoms generally do not occur until levels are below 1 meq/L.[3] Though few patients manage to have levels that low, up to 12% of hospitalized patients present with some degree of hypomagnesemia.[4] Magnesium stores are predominantly in the bone with less than 1% of magnesium in serum.[5] Serum magnesium is also not completely ionized, 20% is protein bound, 65% is ionized, and 15% is complexed with anions.[6]

Calcium and magnesium distribute similarly, and there is a link between magnesium levels and calcium levels, through parathyroid horomone (PTH). PTH secretion is stimulated by low serum magnesium concentrations,[7] and magnesium is needed as a cofactor in PTH function.[8] The relationship between PTH and magnesium is complex, and PTH is not the unique regulator of magnesium balance. Anti-Diuretic Hormone (ADH), calcitonin, glucagon, and insulin are all connected to magnesium homeostasis. PTH is the most important determinant of magnesium balance apart from serum magnesium concentration.[6] Thus hypomagnesemia can often accompanied by a secondary hypocalcemia due to the inability of PTH to function properly despite its reactive increase to low magnesium in the hypomagnesemic patient.[9]

Magnesium wasting can occur in a manner similar to potassium loss. GI losses, diuretics, obligatory urinary loss, and loss through hyperhidrosis can all cause hypomagnesemia. Hypophosphatemia also results in a derangement of magnesium balance by significantly increasing urinary magnesium loss resulting in hypomagnesemia.[6] Loop acting and thiazide diuretics have a very potent effect on magnesium wasting through abrogation of lumen positive potential which prevents magnesium reabsorption through the paracellular route.[10] (See Figure 1 for an illustration of how magnesium reabsorption occurs.) Chronic alcoholism has been known to contribute to

chronic hypomagnesemia as well and maybe difficult to uncover in patients with occult alcohol abuse. This may occur at least partially due to increased urine volume caused by ADH suppression due to alcohol,[11] besides this mechanism other metabolic effects on TRP-M6 [transient receptor potential melastatin type 6][2] or other pathways, which may result in the inappropriate magnesiuria.

Hypomagnesemia symptoms are subtle with small decreases and include fatigue and weakness. Severely low levels cause muscle weakness or hyperactivity depending on concomitant hypocalcemia or hypophosphatemia.[5-7] Tetany with attendant Chovstek's and Trosseau's signs can be seen in hypocalcemia[9] as well as hypomagnesemia, and it is important again to note that the two conditions can often coexist in the patient with muscular dysfunction.[12] Cardiac arrhythmias are the most feared complication and can occur with significant hypomagnesemia. Figure 2 shows the expected pattern of Torsades de Pointes.

Our patient likely has acquired tubular dysfunction due to alcohol use resulting in magnesium loss as well as sodium sensitive thiazide cotransporter inhibition by hydrochlorothiazide that resulted in drop in serum magnesium from baseline of 1.3 to 0.9. His symptoms improved with improvement of magnesium to baseline level though still persistently low. Magnesium remained low despite supplementing almost two times the normal daily magnesium intake (360 mg). Because gut absorption of magnesium is only about 33%, one gram of magnesium supplement daily should have been sufficiently absorbed to meet 73% of the recommended daily intake. The continually low baseline may be due to ongoing tubular dysfunction from persistent alcohol intake or due to an underlying renal magnesium wasting state. Patients with mutations or dysfunction in TRPM6 or SLC41A1 proteins, which regulate magnesium reabsorption can become hypomagnesemic.[13] The syndrome caused by classical mutations in these genes, however, usually presents with hypocalcemia like the classical Hypomagnesemia with secondary hypocalcemia genetic disorder (HSH).[14]

There are other mutations, however, according to a recent review. Naderi et. Al[15] listed several other culprit genes in hypomagnesemic patients. Claudin 16 and 19 mutations (associated with familial hypomagnesemia with hypercalciuria and nephrocalcinosis), a subunit of sodium potassium ATPase on basolateral subunit ADPHH (Autosomal dominant primary hypomagnesemia with hypocalciuria), Epidermal Growth Factor (EGF) mutations (isolated recessive hypomagnesemia with normocalciuria), and Calcium sensing receptor mutations (CaSR) can all result in hypomagesemia. These are rare mutations than the more commonly mutated proteins seen in patients with HSH (TRPM6), Barter's syndrome types I-IV, and Gitelman's syndrome.[15] The mutation that could lead to a presentation of borderline magnesium levels without a family history and with hypercalciuria seen in our patient would be the ADPHH mutation. Please see Table 1 for general classes of mutations leading to renal magnesium wasting states. Cessation of alcohol use, ongoing oral magnesium supplementation as tolerated (due to diarrhea), and parenteral magnesium when needed, along with decreasing magnesiuria with amilioride[15]

are the treatments currently used to raise serum magnesium levels to a level where neurological symptoms subside.

Tables and Figures

Table 1: see attached table legend

| Classes of mutations that can lead to hypomagnesemia with or without other electrolyte disturbances						
Name of genetic syndrome	Trans.	Mutated protein	sCa	sK	uCa	sMg
Barter's syndrome types I-IV (III overlap Barter's and Gitelman's)	AR	NKCC2, Bartin, Basolateral Cl channel	N	L	H	L
Gitelman's syndrome	AR	NCCT	H	L	L	L
Hypomagnesemia with secondary Hypocalcemia (HSH)	AD	TRPM6 or SLC41A1	L	N	L	L
Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC)	AR	Claudin 16, 19	N	N	H	L
Autosomal Dominant Hypomagnesemia with Hypocalciuria (ADPHH)	**AD**	**Na/K Basolateral ATPase**	**N**	**N**	**L**	**L**
Activating CaSR	AD	CaSR	L	N	H	L
Epidermal Growth Factor Mutations	AR	Pro EGF	N	N	N	L

Table legend: CaSR=calcium sensing receptor, Cl=chloride, EGF=epidermal growth factor, H=high, L=low, N=normal, Na=sodium, NCCT=Thiazide-sensitive-sodium-chloride-cotransporter, NKCC2=Sodium-potassium-2 cholride-cotransporter, sCa=serum calcium, sK=serum potassium, SLC41A1=Magnesium transfer protein, Trans=Transmission, TRP-M=transient receptor potential melastatin type 6, uCa=urinary calcium. Note acquired etiologies not listed, see text. BOLD/underlined profile is patient's profile, making presumptive diagnosis of ADPHH.

Figure 1: A) Trend of magnesium level in hospital, B)-E) trends of potassium, sodium, calcium and magnesium during longer term outpatient follow up. A= amilioride 2.5mg started every other day, Etoh=alcohol use, inpt=inpatient intravenous magnesium repletion, IV=intravenous magnesium repletion, MAG= magnesium, mg=milligram, MAG+P=magnesium+protein capsule, mg/dL=milligrams/deciliter, Orange line: 2 alcoholic drinks per day, outpt=outpatient intravenous magnesium repletion, R=fluid/water restrict at1L/day, Red line: 4 alcoholic drinks/day, S= oral magnesium supplementation started, T=thiazide stopped.
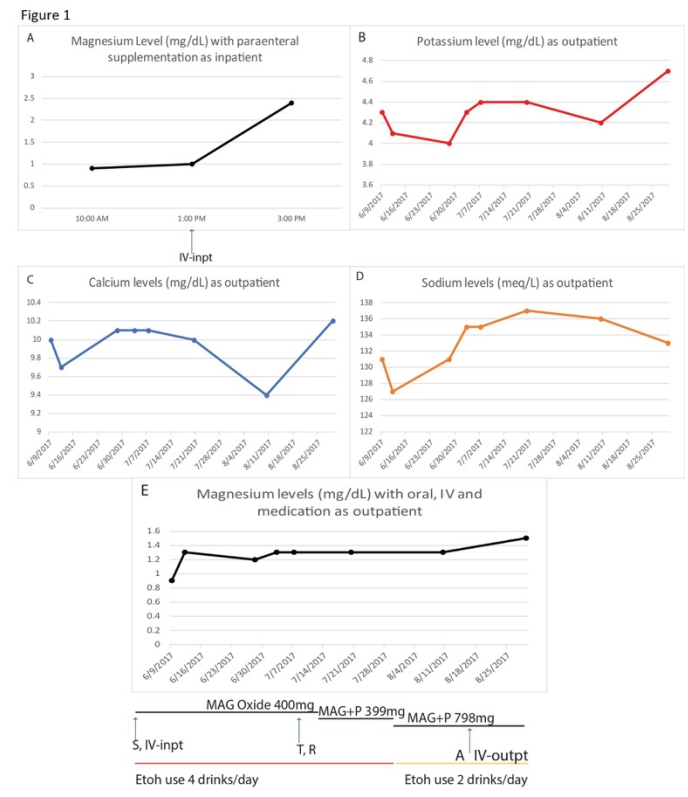
Figure 1

Figure 2: AR=autosomal recessive, CaSR=calcium sensing receptor, Cl=chloride, EGF=epidermal growth factor, EGFR=epidermal growth factor receptor, K=potassium, Na=sodium, NCCT= thiazide-sensitive-sodium-chloride-cotransporter, NKCC2=sodium potassium two chloride channel Mg=magnesium, ProEGF=pro epidermal growth factor, ROMK=renal outer medullary potassium channel, TRP-M=transient receptor potential melastatin type 6, +=positive.

Figure 2
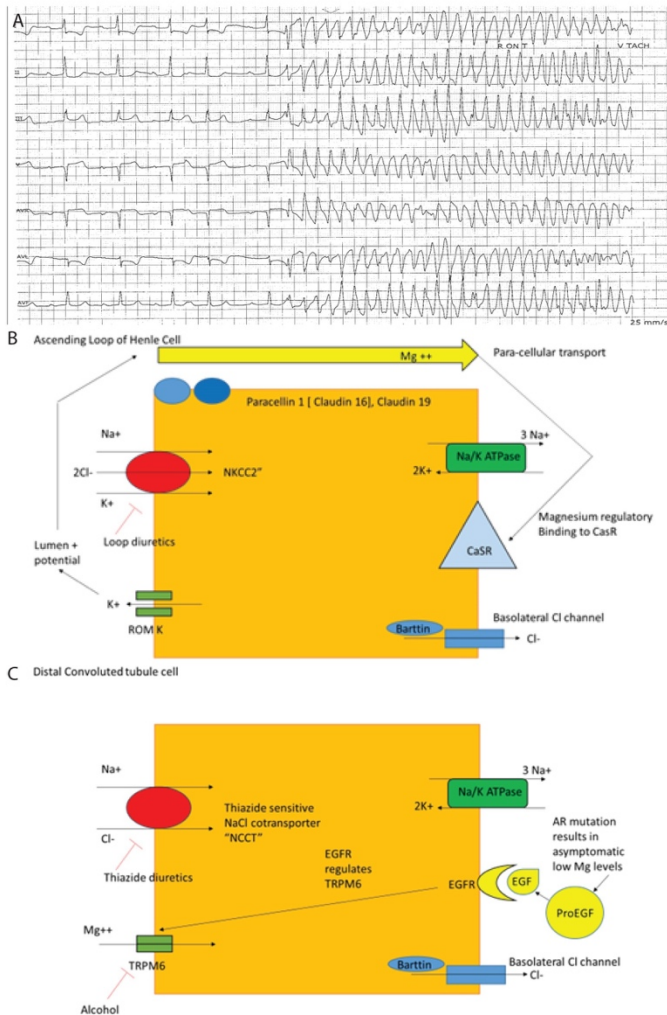
REFERENCES

1. **Ryan MP.** Magnesium- and potassium-sparing effects of amiloride. Review and recent findings. *Magnesium*. 1984;3(4-6):274-88. PubMed PMID: 6536837.

2. **Pham PC, Pham PA, Pham SV, Pham PT, Pham PM, Pham PT.** Hypomagnesemia: a clinical perspective. *Int J Nephrol Renovasc Dis*. 2014 Jun 9;7:219-30. doi:10.2147/IJNRD.S42054. eCollection 2014. Review. PubMed PMID: 24966690; PubMed Central PMCID: PMC4062555.

3. **Ayuk J, Gittoes NJ.** Treatment of hypomagnesemia. *Am J Kidney Dis*. 2014 Apr;63(4):691-5. doi: 10.1053/j.ajkd.2013.07.025. Epub 2013 Oct 4. PubMed PMID:24100128.

4. **Agus ZS.** Hypomagnesemia. *J Am Soc Nephrol*. 1999 Jul;10(7):1616-22. Review. PubMed PMID: 10405219.

5. **Jahnen-Dechent W, Ketteler M.** Magnesium basics. *Clin Kidney J*. 2012 Feb;5(Suppl 1):i3-i14. doi: 10.1093/ndtplus/sfr163. PubMed PMID: 26069819; PubMed Central PMCID: PMC4455825.

6. **Swaminathan R.** Magnesium metabolism and its disorders. *Clin Biochem Rev*. 2003 May;24(2):47-66. PubMed PMID: 18568054; PubMed Central PMCID: PMC1855626.

7. **Paunier L.** Effect of magnesium on phosphorus and calcium metabolism. *Monatsschr Kinderheilkd*. 1992 Sep;140(9 Suppl 1):S17-20. Review. PubMed PMID: 1331782.

8. **Vetter T, Lohse MJ.** Magnesium and the parathyroid. *Curr Opin Nephrol Hypertens*. 2002 Jul;11(4):403-10. Review. PubMed PMID: 12105390.

9. **Martin KJ, González EA, Slatopolsky E.** Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol*. 2009 Nov;20(11):2291-5. doi: 10.1681/ASN.2007111194. Epub 2008 Jan 30. PubMed PMID: 18235082.

10. **Blaine J, Chonchol M, Levi M.** Renal control of calcium, phosphate, and magnesium homeostasis. *Clin J Am Soc Nephrol*. 2015 Jul 7;10(7):1257-72. doi: 10.2215/CJN.09750913. Epub 2014 Oct 6. Review. Erratum in: Clin J Am Soc Nephrol. 2015 Oct 7;10(10):1886-7. PubMed PMID: 25287933; PubMed Central PMCID: PMC4491294.

11. **Elisaf M, Merkouropoulos M, Tsianos EV, Siamopoulos KC.** Pathogenetic mechanisms of hypomagnesemia in alcoholic patients. *J Trace Elem Med Biol*. 1995 Dec;9(4):210-4. PubMed PMID: 8808192.

12. **Williams A, Liddle D, Abraham V.** Tetany: A diagnostic dilemma. *J Anaesthesiol Clin Pharmacol*. 2011 Jul;27(3):393-4. doi: 10.4103/0970-9185.83691. PubMed PMID: 21897517; PubMed Central PMCID: PMC3161471.

13. **de Baaij JHF, Schlingmann KP, Burtey S, Thomassen M, van der Wijst J, Knoers N, Bindels RJM, Konrad M, Hoenderop JGJ.** A heterozygous de novo mutation in SLC41A1 causes hypomagnesemia and renal magnesium wasting. *FASEB Journal* 2017; 31(1).

14. **Astor MC, Løvås K, Wolff AS, Nedrebø B, Bratland E, Steen-Johnsen J, Husebye ES.** Hypomagnesemia and functional hypoparathyroidism due to novel mutations in the Mg-channel TRPM6. *Endocr Connect*. 2015 Dec;4(4):215-22. doi: 10.1530/EC-15-0066. Epub 2015 Aug 13. PubMed PMID: 26273099; PubMed Central PMCID: PMC4566842.

15. **Naderi AS, Reilly RF Jr.** Hereditary etiologies of hypomagnesemia. *Nat Clin Pract Nephrol*. 2008 Feb;4(2):80-9. doi: 10.1038/ncpneph0680. Review. PubMed PMID: 18227801.