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Seizures Related to Hypomagnesemia: A Case Series and Review of the Literature

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Abstract

Objective: Childhood seizures have various nonneurological etiologies. The patient's magnesium levels should be measured when evaluating afebrile seizures. The purpose of the current case series is to describe a systematic approach for diagnosing hypomagnesemia using 3 recent patient cases. **Methods:** This case series describes 3 patients with unprovoked hypomagnesemia-associated seizures. The authors describe the differential diagnosis, pathophysiology, and the workup of hypomagnesemia-associated seizures. **Results:** Hypomagnesemia contributed to the cause of the seizures in all 3 cases. Various causes of hypomagnesemia were investigated, including genetic etiologies. All 3 patients were maintained at a magnesium level >0.65 mmol/L, which improved or eliminated the seizures. **Significance:** Magnesium levels should always be measured when trying to determine the etiology of seizures. Hypomagnesemia and afebrile seizures should be treated with the goal of maintaining a magnesium concentration >0.65 mmol/L. Although rare, genetic causes of hypomagnesemia should be considered, once common causes of hypomagnesemia are ruled out.

Keywords

seizures, hypomagnesemia with secondary hypocalcemia, *TRPM6*, isolated recessive hypomagnesemia, Galloway-Mowat syndrome

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Background

The standard workup for afebrile seizures includes measuring calcium, glucose, and electrolytes, which comprises magnesium, despite the fact that routine serum chemistries may be of extremely low diagnostic yield.[1] Hypomagnesemia is an uncommon cause of seizures[2] and can be overlooked in the emergency department or outpatient setting when a patient presents with a seizure. The prevalence of seizures in children with known causes of hypomagnesemia is 16%.[1]

The incidental finding of hypomagnesemia during a seizure workup should be investigated and treated. In addition to validating the low serum magnesium, checking other electrolytes such as serum calcium, assessing renal function via, among other diagnostic tools, a renal ultrasound to rule out medullary nephrocalcinosis, and investigating endocrine function are all helpful in determining the underlying causes. Acquired or genetic disorders can be the underlying cause of the magnesium abnormality. A couple of common secondary or genetic causes include poor gastrointestinal absorption and excessive renal wasting.[3,4]

In this study, the authors describe 3 cases where the leading symptom was afebrile seizures. These case reports focus on the

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diagnostic algorithm and patient management. The authors also discuss the value of genetic testing in this context.

Patients and Methods

This study was exempt from research ethics approval because it included fewer than 5 cases. The authors obtained informed written consent for inclusion in the case series in each case. The participants were from a single center. A retrospective chart review was used to collect all data. Patients' anthropometry was assessed using the Centers for Disease Control and Prevention growth charts, and data were expressed as percentiles. Patients' data and laboratory values were obtained from the patients' electronic medical records. Data are expressed using the International System of Units, followed by the reference interval in square brackets and imperial measurement in regular brackets.

Case Reports

Case 1

The patient was a 23-month-old female with normal development. She had a noncontributory history and nonconsanguineous parents. Her family history was negative for both epilepsy and neurological abnormalities, as well as any known renal, thyroid, or parathyroid disease. Previously healthy, she presented with her first tonic seizure (15 seconds in length) following 2 days of vomiting and dehydration. She had low serum magnesium, <0.08 [reference interval 0.65-1.05] mmol/L (<0.16 mg/dL), and a serum calcium concentration of 1.52 [reference interval 2.15-2.55] mmol/L (6.08 mg/dL) and was referred to a pediatric endocrinologist. The hypomagnesemia and hypocalcemia were presumed to be secondary to decreased nutrition and gastroenteritis.

She required admission and intravenous hydration upon presentation. Forty-five milligrams of oral magnesium gluconate thrice daily, 1000 mg of calcium carbonate once daily, and 1000 U of vitamin D3 once daily were initiated to treat her hypomagnesemia and hypocalcemia. One month later, she presented with a 2-minute generalized tonic seizure devoid of infectious symptoms or fever while still taking the magnesium supplement. Results from the anthropometric measurements and physical were noncontributory and she had no dysmorphic or neurocutaneous features. Her serum magnesium level was once again abnormally low at 0.14 [reference interval 0.65-1.05] mmol/L (0.34 mg/dL), and she had a low serum calcium concentration of 1.67 [reference interval 2.15-2.55] mmol/L (6.68 mg/dL). Her magnesium fractional excretion was elevated at 300% under conditions of hypomagnesemia. Her serum bicarbonate, serum potassium, urate, fractional potassium excretion, urinary amino acids, and low-molecular-weight proteinuria results were normal, but she had hypercalciuria with a urinary calcium/creatinine ratio of 2.04 [reference interval < 0.6] mmol/mmol. Cerebral spinal fluid, blood, and urine cultures revealed no growth. The results of both an electroencephalogram (EEG) and a cerebral computed tomography (CT) scan were normal so she was not given anticonvulsants. A renal ultrasound did not show any nephrocalcinosis. Genetic testing revealed 2 genetic variants in the *TRPM6* gene (c.2529G>A [p.Trp843*] and c.5359A>C [p.Ser1787Arg]). c.2529G>A [p.Trp843*] is associated with autosomal recessive familial hypomagnesemia with secondary hypocalcemia in the homozygous state, and c.5359A>C [p.Ser1787Arg] has not been previously reported and is of uncertain significance, although it can be pathogenic since this variant is in the MHSK/EF2 kinase domain.

She initially received intravenous magnesium sulfate (25 mg/kg), which normalized her serum magnesium and prevented any subsequent seizures. Her hypomagnesemia normalized and she maintained magnesium levels around 0.73 mmol/L (1.78 mg/dL). Her serum and urinary calcium levels also normalized with magnesium supplementation. She was transitioned to oral magnesium oxide (110 mg/kg/d in 3 divided doses) by discharge, which she tolerated without diarrhea. She has not had any subsequent seizures on follow-up at 8 years of age, but she requires higher doses of oral magnesium during febrile illnesses. Her neurodevelopment has been normal.

Case 2

The second patient was a 13-month-old female. Following a pregnancy without any complications, including an absence of polyhydramnios, she was born at term to a 32-year-old G2P2 mother and nonconsanguineous parents. Her family history revealed a paternal aunt who had had seizures as a child but no other family members had any known renal diseases. The child had an unremarkable history with no past episodes of dehydration or poor growth. Her sole neurodevelopmental symptom was a speech delay, and her physical examination was noncontributory. She presented with seizures and a low magnesium level, which required consultations with various health-care providers including a pediatric neurologist. Although there was no workup for hypomagnesemia, an EEG was performed, which showed 5-Hz generalized spikes and waves during sleep. The results of 2 brain magnetic resonance imaging (MRI) scans showed nonspecific changes in the white matter bilaterally. A pediatric neurologist recommended anticonvulsant therapy in the event of another seizure.

The patient did not present with another seizure until the age of 7, when she was ill with a febrile respiratory illness positive for influenza B and had seizures that were accompanied by a profound hypomagnesemia. Her growth parameters were within normal limits: weight (33.5 kg), height (132.5 cm), and head circumference (62 cm) were near the 90th percentile. She did not exhibit any dysmorphic or neurocutaneous features. A renal ultrasound did not show any medullary nephrocalcinosis. She had a low magnesium level, 0.29 mmol/L [reference interval 0.65-1.05] (0.71 mg/dL), and a low ionized calcium level, 0.69 [reference interval 1.09-1.30] mmol/L (2.76 mg/dL). Her fractional excretion of magnesium was elevated at >10% with correction and she had hypercalciuria (calcium/creatinine ratio 0.70 [reference interval <0.6] mmol/mmol). The results of all other tests were normal. A genetic analysis was performed for the *TRPM6* gene and revealed a novel heterozygous, possibly

pathogenic but synonymous, variant of the gene (c.2538G>A [p.Thr846Thr]). Software analysis (Alamut v2.7.1) predicted that an aberrant effect on splicing was likely. There was also 1 unknown variant in the *SLC4A4* gene, which encodes a sodium bicarbonate cotransporter in the kidney and eye (Online Mendelian Inheritance in Man, OMIM 603345 [www.omim.org]), of uncertain clinical significance (c.2622-23G>A).

The patient improved with intravenous magnesium sulfate (25 mg/kg), and she maintained a stable magnesium level of 0.61 mmol/L (1.48 mg/dL) following a transition to oral magnesium oxide (75 mg/kg/d) and the addition of amiloride (0.15 mg/kg/d). Her serum and urinary calcium and magnesium levels also returned to normal. She has not had a follow-up brain MRI since her magnesium levels normalized. She remains well on follow-up without the recurrence of seizures while on magnesium oxide and amiloride but also requires higher magnesium levels during febrile illnesses. She has not been taking any seizure medications and has been seizure-free for over 2 years.

Case 3

The last patient was a 4-year-old female. Following an uncomplicated pregnancy with no ultrasound abnormalities or polyhydramnios, she was born to a G1P1 mother and nonconsanguineous parents. The patient's mother had had a history of renal stones and recurrent urinary tract infections secondary to a vesicoureteral reflux. The maternal great uncle had received a renal transplant in his mid-40s, though the reason for the transplant was unknown. There was no other family history of renal disease or hearing loss. The child had a longstanding history of dysmorphic features and spastic dystonic diplegia. Her symptoms were consistent with those found on the Galloway-Mowat syndrome spectrum and included microcephaly, cerebellar atrophy, developmental delay and seizures, and proteinuria, with an absence of infantile nephrotic syndrome. Her dysmorphic features included prominent large ears, frontal bossing, a broad nasal bridge, a high arch palate, and scarce eyebrows. In the past, she had exhibited failure to thrive and developmental delay that had progressed since the age of 8 months. She was followed by the genetics clinic because of her developmental delay and her dysmorphic features, which could not be linked to a particular diagnosis or syndrome. She had no previous episodes of dehydration, polyuria, or polydipsia.

She initially presented with status epilepticus and hypomagnesemia at the age of 4. Her anthropomorphic parameters were within normal limits: weight (10.0 kg—below the 3rd percentile), height (94 cm—between the 3rd and 10th percentiles), and head circumference (44.5 cm—below the 3rd percentile). She was placed on valproic acid following her first seizure and experienced significant side effects including lethargy and severe drooling.

She had 2 subsequent hypomagnesemia-associated episodes of status epilepticus; her most recent episode had been complicated by an extended spectrum β-lactamase *Escherichia coli* urinary tract infection. Her lowest magnesium level was 0.31 mmol/L [reference interval 0.65-1.05] (0.75 mg/dL) and her calcium level was normal at 2.31 mmol/L [reference interval 2.15-2.55] (9.24 mg/dL). Her fractional excretion of magnesium was elevated at 26%. There was no evidence of hypercalciuria (calcium to creatinine ratio 0.35 [reference interval < 0.6] mmol/mmol). Aside from transiently low serum potassium, her serum bicarbonate level, urate level, and fractional potassium excretion were normal. Exome sequencing was performed to verify the *CNNM2* mutation differential diagnosis, which is associated with hypomagnesemia and impaired brain development. This test was negative and there was no association with any other known magnesium-losing tubulopathies. No abnormalities were noted in the *WDR73* gene, which is associated with Galloway-Mowat syndrome. A head MRI revealed diffuse cerebral white matter signal abnormalities evocative of demyelination along with progressive atrophy of the cerebellar hemispheres. The numerous EEGs that were performed while she took her maintenance antiepileptics showed that her epileptic activity ceased when her magnesium levels normalized. Her EEG had a background of δ grade II generalized activity, with suppression of grade I activity in the right hemisphere.

The patient's seizures were difficult to control, requiring phenytoin (15 mg/kg loading dose) and intubation with a midazolam infusion during her episodes of status epilepticus. Her serum magnesium levels normalized after several days of magnesium sulfate infusions (14 mg/kg/h), after which she was switched to oral magnesium oxide (120 mg/kg/d). The addition of amiloride was necessary to maintain stable magnesium levels, and following another episode of status epilepticus, some of the magnesium oxide was replaced with magnesium bisglycinate to reduce diarrhea. If her magnesium levels fall below 0.65 mmol/L, she usually experiences seizures. She is also on enalapril to control her hypertension and proteinuria, which are commonly seen in Galloway-Mowat syndrome.

Discussion

The mechanism behind hypomagnesemia-causing seizures is not well understood.[3] It has been proposed via rat models that a reduction in extracellular magnesium results in a lack of antagonism at the *N*-methyl-D-aspartate-type glutamate receptors, thereby resulting in epileptiform discharges.[5]

Diagnosis—Nonhereditary

Hypomagnesemia is a common finding, with a prevalence of up to 12% in hospitalized patients.[6] Common signs and symptoms of hypomagnesemia include those of cardiac and neuromuscular origin. Electrocardiographic changes and arrhythmias result from intracellular hypokalemia due to impairment of the Na^+-K^+-ATPase, which results from hypomagnesemia.[7] Symptoms of neuromuscular irritability include muscle twitching, tetany, and positive Chvostek and Trousseau signs. Hypomagnesemia also causes seizures.

Table 1. Causes of Hypomagnesemia (Excluding Inherited Etiologies).

Gastrointestinal	Renal	Other
Decreased dietary intake Increased loses • Acute or chronic diarrhea • Steatorrhea Decreased absorption • Primary intestinal hypomagnesemia • Inflammatory bowel disease Other: • Acute pancreatitis	Medications • Loop and thiazide diuretics • Aminoglycosides • Amphotericin B • Cisplatin • Cyclosporine • Proton pump inhibitors Tubular dysfunction • Recovery after acute tubular injury • Postobstructive diuresis Other • Hypercalcemia • Volume expansion • Primary aldosteronism	Hungry bone syndrome • Postparathyroidectomy • Postthyroidectomy After correction systemic acidosis

Table 2. Inherited Disorders of Renal Magnesium Handling.[a]

Disorder	OMIM #	Inheritance	Gene Locus	Gene	Protein
Gitelman syndrome	263800	AR	16q13	*SLC12A3*	NCCT, Na^+-Cl^- cotransporter
Isolated dominant hypomagnesemia	154020	AD	11q23	*FXYD2*	Gamma-subunit of the Na^+-K^+-ATPase
Isolated recessive hypomagnesemia	611718	AR	4q25	*EGF*	Pro-epidermal growth factor
Autosomal dominant hypocalcemia, autosomal dominant hypoparathyroidism	146200	AD	3q21	*CASR*	CaSR, Ca^{2+}/Mg^{2-} sensing receptor
Familial hypocalciuric hypocalcemia, familial benign hypercalcemia	145980	AD	3q21	*CASR*	CaSR, Ca^{2+}/Mg^{2-} sensing receptor
Neonatal severe primary hyperparathyroidism	239200	AR	3q21	*CASR*	CaSR, Ca^{2+}/Mg^{2-} sensing receptor
Familial hypomagnesemia with hypercalciuria/nephrocalcinosis	248250	AR	3q28	*CLDN16*	Claudin-16 (paracellin-1) tight junction protein
Familial hypomagnesemia with hypercalciuria/nephrocalcinosis and severe ocular involvement	248190	AR	1p34	*CLDN19*	Claudin-19 tight junction protein
Hypomagnesemia with secondary hypocalcemia	602014	AR	9q22	*TRPM6*	TRPM6, Mg^{2+} channel
Hypomagnesemia/metabolic syndrome	500005	Maternal	mtDNA	*MTTI*	Mitochondrial tRNA (isoleucine)
Hypomagnesemia with seizures and mental retardation	607803	AR, AD	10q24.32	*CNNM2*	Mg^{2+} channel

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.
[a] Modified with permission from Avner et al.[12]

When faced with hypomagnesemia, various nonhereditary etiologies, primarily gastrointestinal or renal—see Table 1—should first be considered. These etiologies include (1) a significant reduction in magnesium intake or intestinal malabsorption (primary or secondary to inflammatory bowel disease[8]) or losses; (2) acute pancreatitis (via magnesium saponification in necrotic fat, similar to the mechanism responsible for the associated hypocalcemia); (3) the administration of medications (such as loop diuretics), antineoplastic agents (such as cisplatin), calcineurin inhibitors (such as cyclosporine and aminoglycosides),[9] or proton pump inhibitors (which involves the inhibition of magnesium absorption via transient receptor potential melastin [*TRPM*] 6 and 7 cation channels)[10,11]; (4) either volume expansion or hypercalciuria (decreases passive magnesium transport); and (5) ''hungry bone syndrome'' postparathyroidectomy and postcorrection of systemic acidosis.[9] Medications can also cause hypermagnesuria either by increasing magnesium secretion or by inducing tubular damage. Other investigations should include measuring the parathyroid hormone, alkaline phosphatase, aldosterone, and renin to rule out endocrine etiologies.

Diagnosis—Hereditary

Still, finding a noninherited cause for hypomagnesemia does not rule out the coexistence of an inherited etiology (see Table 2). Some baseline investigations, including extended serum and urine electrolyte panels, blood gas, renal ultrasound

Table 3. Clinical and Biochemical Characteristics of Inherited Hypomagnesemia.[a]

Disorder	Age at Onset	Serum Mg^{2+}	Serum Ca^{2+}	Serum K^{+}	Blood pH	Urine Mg^{2+}	Urine Ca^{2+}
Gitelman syndrome	Adolescence	↓	N	↓	↑	↑	↓
Isolated dominant hypomagnesemia	Childhood	↓	N	N	N	↑	↓
Isolated recessive hypomagnesemia	Childhood	↓	N	N	N	↑	N
Autosomal dominant hypocalcemia, autosomal dominant hypoparathyroidism	Infancy	↓	↓	N	N or ↓	↑	↑-??
Familial hypocalciuric hypocalcemia, familial benign hypercalcemia	Often asymptomatic	N to ↑	↑	N	N	↓	↓
Neonatal severe primary hyperparathyroidism	Infancy	N to ↑	↑↑↑	N	N	↓	↓
Familial hypomagnesemia with hypercalciuria/ nephrocalcinosis	Childhood	↓	N	N	N or ↓	↑↑	↑↑
Hypomagnesemia with secondary hypocalcemia	Infancy	↓↓↓	↓	N	N	↑	N

Note. N indicates neutral, ↑ indicates raises, and ↓ indicates lowers.
[a] Modified with permission from Avner et al.[12]

for nephrocalcinosis, and a hearing test, can offer valuable clues to inherited etiologies. For instance, alkalosis, hypokalemia, hypocalciuria, and hypermagnesuria can suggest Bartter, Gitelman, or full-spectrum epilepsy ataxia sensorineural deafness tubulopathy syndrome.[13] Table 3 outlines pertinent clinical and biochemical features of inherited hypomagnesemia.

There have been a number of cases where seizures were the prominent feature of inherited hypomagnesemia.[14-17] Zhao et al[17] described 2 sisters with familial hypomagnesemia and secondary hypocalcemia characterized by a *TRPM6* gene mutation, the gene that was affected in the first and second patients. *TRPM6* encodes an apical Mg^{2+} channel in the colon, and the distal convoluted tubule and mutations in this gene can cause the most profound genetic hypomagnesemia.[13] These patients often present with seizures within their first few months of life. An early diagnosis of the underlying hypomagnesemia is likely to ameliorate patients' neurological and cognitive outcomes. Additionally, Lainez et al[18] sequenced this gene in 7 patients from 5 unrelated families who presented with hypomagnesemia and secondary hypocalcemia and identified homozygous or compound heterozygous mutations in each patient.

CNNM2 is most highly expressed in the distal convoluted tubule, in the thick ascending limb in the loop of Henle, and in the brain.[13] This gene can play a role in renal magnesium handling, brain development, and neurological functioning.[19] Recently, Arjona et al identified this mutation in 5 families with mental retardation, seizures, and hypomagnesemia. Although the genetic testing in the third patient was negative for any abnormality in the *CNNM2* gene,[19] she has features that are consistent with Galloway-Mowat syndrome (OMIM 251300) and it is possible that she has a variation of this syndrome and that one of its renal manifestations is magnesium-losing tubulopathy.

Treatment

In addition to receiving appropriate anticonvulsant therapy to cease the seizures, a patient presenting with hypomagnesemia and seizures should be given intravenous magnesium sulfate over the course of 24 hours. It can be given in single intravenous boluses (neonate: 25 mg/kg/dose every 8-12 hours; child: 20-200 mg/kg/dose every 4-6 hours, maximum 2 g/dose).[20] The rate of infusion should not exceed 125 mg/kg/h. This treatment can cause facial flushing, hypotension, and atrioventricular block, so some patients should receive continuous cardiorespiratory monitoring.[21] Chronic magnesium replacement in children usually requires a dose of 10 to 20 mg Mg^{2+} (0.4-0.8 mmol) per kg, 3 to 4 times per day.[22] Various oral magnesium supplements are available, including magnesium oxide, magnesium gluconate, and magnesium glucoheptonate. High doses can cause diarrhea and electrolyte abnormalities so electrolytes should be monitored regularly. Amiloride or triamterene can sometimes be added if magnesium levels cannot be stabilized through oral supplementation alone. These agents can increase magnesium reabsorption in the collecting tubules.[23]

Summary

These 3 case studies demonstrate the importance of recognizing magnesium deficiency as a rare but important cause of seizures. Although this is well known within medicine, the case studies build upon this principle by conveying important lessons to practicing physicians that have been unearthed through the experience gained in treating real-world cases. First, when presented with a seizure, physicians should test for hypomagnesemia and, if confirmed, should trigger a workup that includes underlying genetic causes of magnesium wasting rather than attributing the hypomagnesemia to dehydration or to a viral illnesses. A referral to a pediatric nephrologist, pediatric neurologist, and, if applicable, a genetic counselor or geneticist are helpful in this case. Second, genetic testing can play a very important role in confirming the disorder, in understanding the pathophysiology of the disease, and in informing the therapeutic approach. Lastly, magnesium supplementation

can effectively control hypomagnesemia-caused seizures in a significant proportion of patients.

Authors' Note

The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Author Contributions

BBC and MK drafted the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. CP reviewed and revised the manuscript and approved the final manuscript as submitted. CC provided his expertise for components of the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. GF conceptualized the idea for the manuscript, provided his expertise for components of the manuscript, drafted the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Declaration of Conflicting Interests

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