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17q12 Microdeletion Syndrome Presenting With Refractory Hypomagnesemia and Diabetes: A Case Report

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Mansumeet Singh [1], Caroline Wang [2], Usha Ravi [3], Harikrishna Choudary Ponnam [4], Rahul Kashyap [5]

1. Nephrology, Premier Renal Care Associates, Cuyahoga Falls, USA 2. Nephrology, Drexel University College of Medicine, Philadelphia, USA 3. Pediatrics, Pediatric Associates, Visalia, USA 4. Internal Medicine, Summa Health, Akron, USA 5. Research, Wellspan York Hospital, York, USA

Corresponding author: Caroline Wang, cw3238@drexel.edu

Abstract

The 17q12 microdeletion syndrome can be inherited in an autosomal dominant manner, although most cases of the syndrome are a result of a de novo mutation. Among the more common features associated with this chromosomal change are problems with the development or function of the kidneys and urinary system. These problems can range from severe malformations of the kidneys or kidney failure before birth to mild or no problems with the kidney or urinary bladder. Characteristic features include maturity-onset diabetes of the young 5 (MODY5), speech developmental delays, intellectual disability, and neuropsychiatric disorders like schizophrenia, anxiety, and bipolar disorder. We present a patient who had uncontrolled diabetes with hypomagnesemia. More common causes of hypomagnesemia are gastrointestinal losses, poor gastrointestinal absorption, proton-pump inhibitors, diuretics, and renal losses due to nephrotoxins or tubular dysfunction. Rarely, as in this case, hypomagnesemia was caused by renal magnesium wasting.

Categories: Internal Medicine, Nephrology, Endocrinology/Diabetes/Metabolism
Keywords: 17q12 microdeletion syndrome, hypomagnesemia, kidney function, maturity-onset diabetes of the young, renal cysts and diabetes syndrome

Introduction

Hypomagnesemia can be caused by gastrointestinal losses, poor gastrointestinal absorption, proton pump inhibitor (PPI) and diuretic use, and renal losses due to nephrotoxins or acquired or inherited tubular dysfunction [1]. 17q12 microdeletion syndrome is a rare genetic condition caused by a 1.06-2.46 Mb deletion at chromosome 17q12, which commonly includes the *HNF1B* gene and can result in renal magnesium wasting [2]. The chromosome segment commonly deleted contains 15 genes; two of which, *HNF1B* and *LHX1*, are thought to underlie some of the features of 17q12 microdeletion syndrome [2]. While the signs and symptoms of this condition can vary greatly among patients, the syndrome is generally characterized by three core features: structural or functional abnormalities of the kidney and urinary tract, maturity-onset diabetes of the young type 5 (MODY5), and neurodevelopmental or neuropsychiatric disorders [3]. Common structural abnormalities of the kidney include cystic or dysplastic kidneys [4]. Other kidney abnormalities include tubulointerstitial disease characterized by reduced urine concentrating ability, absent to minimal proteinuria, hyperuricemia, hypomagnesemia, and hypokalemia. In some cases, hypomagnesemia is the initial and predominant presentation of kidney disease [3,4]. This is a rare genetic cause of hypomagnesemia due to renal magnesium wasting.

Case Presentation

A 38-year-old white female with a past medical history of uncontrolled diabetes mellitus since 2001 and no significant family history was referred to the outpatient clinic for refractory hypomagnesemia. She required high-dose oral magnesium supplementation and occasional IV magnesium supplementation when the levels dropped below 0.8 mg/dL (normal range 1.7-2.4 mg/dL). However, she was asymptomatic from a hypomagnesemia standpoint.

The evaluation of this patient's hypomagnesemia began by confirming low serum magnesium and assessing associated electrolyte abnormalities, including potassium, calcium, and phosphate levels, as well as renal function. The patient's serum magnesium was persistently low, ranging from 0.8-1.2 mg/dL (normal range 1.7-2.4 mg/dL). However, she did not have any other electrolyte abnormalities. She also had normal renal function (serum creatinine (Cr) < 1).

The next step was distinguishing between gastrointestinal magnesium loss, inadequate intake, and renal magnesium wasting. The patient denied alcohol use and did not use any diuretics, PPIs, or nephrotoxic drugs. She had no malabsorption syndromes or history of abdominal surgery.

To further distinguish between the potential causes of hypomagnesemia, a 24-hour urinary magnesium

measurement was done. This test helps determine if the kidneys are appropriately conserving magnesium in hypomagnesemia. A 24-hour urinary magnesium excretion less than approximately 10-12 mg/day suggests appropriate renal conservation and favors gastrointestinal loss or reduced intake, while urinary magnesium excretion greater than approximately 24 mg/day suggests inappropriate renal magnesium loss. This patient's 24-hour urine magnesium excretion was 181 mg/day, which is suggestive of renal magnesium wasting. Results of the urine magnesium study are shown in Table *1*.

Parameter	Patient's Value	Reference Range
Volume (mL)	2100	800-2000
Urine Magnesium (mg/dl)	8.6	1.2-18.7
Urine Magnesium (mg/day)	181	12-199
Urine creatinine (mg/dl)	60	20-275
Urine Creatinine (mg/day)	1260	700-1600

TABLE 1: 24-hour urine magnesium study

For management of her persistent hypomagnesemia, the patient was started on oral magnesium oxide supplementation and amiloride 5 mg daily throughout the year. The patient had partial adherence to these medications due to side effects, including gastrointestinal upset and hypotension, which precluded consistent dosing. Given the patient's presentation of renal magnesium wasting, persistent hypomagnesemia, and associated diabetes, all features suggestive of *HNF1B*-associated disease, genetic testing was done for diagnosis. Genetic testing revealed a 17q12 deletion, a very rare cause of hypomagnesemia due to renal magnesium wasting, and the patient was referred to the genetics clinic.

Despite best medical management, the patient's magnesium levels ran between 0.8-1.2 mg/dL (normal range 1.7-2.4 mg/dL). She remained clinically stable with persistently low but tolerable levels of magnesium, requiring intermittent IV replacement. Upon last follow-up in September 2025, the patient was noted to be asymptomatic with magnesium levels of 0.9 mg/dL. The goal was to maintain magnesium levels at or above 0.8 mg/dL, which the patient met. Since the diagnosis of 17q12 microdeletion syndrome, the patient has followed with a geneticist, endocrinologist, audiologist, urologist, and gynecologist. A recent colonoscopy was negative for acute findings. Renal ultrasound done recently showed left renal atrophy, left nephrolithiasis, and a complex renal cyst (Figure *1*). Both the nephrolithiasis and cyst are being conservatively monitored by urology.

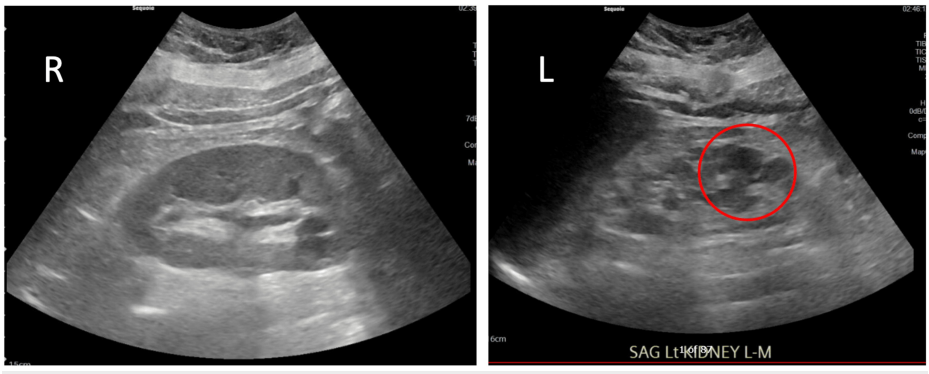


FIGURE 1: Renal ultrasound showing a complex renal cyst in the left kidney

Discussion

This patient with uncontrolled diabetes mellitus had asymptomatic refractory hypomagnesemia with normal renal function and no obvious underlying etiology. Further workup and genetic testing revealed 17q12 microdeletion syndrome as the cause of hypomagnesemia, which was secondary to renal magnesium wasting.

The 17q12 microdeletion syndrome presents with variable phenotypes. These include multicystic dysplastic

kidneys or other urinary system anomalies, pancreatic dysfunction (MODY5), and neurodevelopmental disorders such as intellectual disability, autism, speech delay, and schizophrenia [5]. Patients with mutations in the *HNF1B* gene, a gene commonly affected by 17q12 microdeletion syndrome, are often present with similar phenotypes. *HNF1B* is a transcription factor that regulates the expression of multiple genes involved in the morphogenesis of the kidneys, pancreas, genitalia, liver, thymus, and gut [4]. As a result, individuals with *HNF1B* loss-of-function mutations often present with renal cysts and MODY5 [4].

Additionally, defects in *HNF1B* affect renal magnesium handling in the distal convoluted tubule, where magnesium is reabsorbed through the transient receptor potential melastatin type 6 (TRPM6) channels to determine the final urinary magnesium excretion [6]. This process is mediated by the voltage gradient created by the Na/K ATPase. HNF1B also represses *FXYD2*, a gene that encodes the gamma subunit of the sodium-potassium adenosine triphosphatase (Na/K ATPase) [7]. Therefore, mutations in *HNF1B* can result in hypomagnesemia due to renal wasting. Wang et al. found that patients with whole-gene *HNF1B* deletion were more likely to have hypomagnesemia than those with intragenic mutations [7]. Since hepatocyte nuclear factor (HNF) homeoproteins form heterodimers in the distal convoluted tubule to regulate magnesium reabsorption, this suggests that haploinsufficiency, rather than dominant-negative mechanisms, underlies magnesium wasting [7].

The genetic basis of congenital kidney anomalies is heterogeneous. While *HNF1B* deletions cause cystic disease and tubular dysfunction, other genetic defects such as those affecting left-right axis patterning (ZIC3, ACVR2B, CFC1) can result in structural anomalies like unilateral renal agenesis, sometimes in association with polysplenia [8]. This heterogeneity underscores the value of genetic testing in unexplained congenital kidney disease.

The 17q12 microdeletion syndrome is a rare but increasingly recognized cause of refractory hypomagnesemia, so there is limited published literature on the presentation and management of the condition. Although hypomagnesemia is often considered a late manifestation of the disease, van der Made et al. and Velamakanni et al. reported cases where hypomagnesemia was the initial and predominant presentation [6, 9]. This patient also highlights a case of renal magnesium wasting in the absence of impaired kidney function.

Typical first-line pharmacologic management of chronic hypomagnesemia in the outpatient setting is oral magnesium supplementation [10]. Additionally, adjunctive agents including potassium-sparing diuretics like amiloride can be used to help enhance renal tubular magnesium reabsorption [10]. However, long-term management of hypomagnesemia with these agents is complicated by their side effects, as was the case with this patient. The effectiveness of oral magnesium supplementation is limited by its gastrointestinal side effects, including nausea, diarrhea, and abdominal cramping [10]. The use of potassium-sparing diuretics is limited by side effects like hypotension. When oral supplementation and adjunctive therapies fail to adequately treat hypomagnesemia, parenteral therapy may be indicated [11]. This was the case with this patient, who remains clinically stable with persistently low but tolerable magnesium levels, requiring intermittent IV replacement.

Conclusions

This case illustrates a rare genetic etiology of refractory hypomagnesemia (17q12 deletion/*HNF1B*-related nephropathy). Though rare, 17q12 microdeletion syndrome should be considered in patients whose clinical histories do not align with more common causes of hypomagnesemia, like alcohol use, malabsorption syndromes, or the use of proton pump inhibitors, diuretics, or nephrotoxins. Additional work-up for 17q12 microdeletion syndrome with genetic testing should be considered in patients presenting with renal magnesium wasting, persistent hypomagnesemia, and associated diabetes mellitus, particularly when accompanied by renal abnormalities or other features suggestive of *HNF1B*-associated disease. In this patient, hypomagnesemia with normal kidney function was one of the predominant presentations of the disease, along with her history of diabetes. Her presentation emphasizes the importance of genetic testing in unexplained renal magnesium wasting, particularly in patients with coexisting diabetes and normal renal function.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Caroline Wang, Mansumeet Singh, Usha Ravi, Harikrishna Choudary Ponnam

Drafting of the manuscript: Caroline Wang, Mansumeet Singh, Usha Ravi, Harikrishna Choudary Ponnam

Concept and design: Mansumeet Singh, Rahul Kashyap

Critical review of the manuscript for important intellectual content: Mansumeet Singh, Rahul Kashyap

Supervision: Rahul Kashyap

Disclosures

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