Hypomagnesemia as First Clinical Manifestation of ADTKD-HNF1B: A Case Series and Literature Review

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Key Words

HNF1B · Hypomagnesemia · RCAD · MODY5 · CAKUT · ADTKD-HNF1B

Abstract

Background: Autosomal dominant tubulointerstitial kidney disease subtype HNF1B (ADTKD-HNF1B) is caused by a mutation in hepatocyte nuclear factor 1 homeobox beta (*HNF1B*). Although 50–60% of ADTKD-HNF1B patients develop hypomagnesemia, *HNF1B* mutations are mainly identified in patients with structural kidney defects or diabetes. **Cases:** The current case series describes 3 patients in whom hypomagnesemia proved to be the first clinical manifestation of ADTKD-HNF1B. All patients presented with hypomagnesemia with a high fractional excretion of Mg^{2+} and hypocalciuria. Exome sequencing performed for analysis of known and candidate hypomagnesaemia genes and subsequent multiplex ligation-dependent probe amplification analysis revealed a large deletion at the chromosome 17q12. Follow-up analysis showed increased blood glucose concentrations in all 3 patients and high hemoglobin A1c levels in 2 out of 3 patients, indicating diabetes mellitus. Although all

patients suffered from mild renal insufficiency, only 1 of the 3 patients was shown to have renal cysts on CT. **Conclusion:** The prevalence of *HNF1B* mutations and the relative contribution of hypomagnesemia to its symptoms are underestimated. Therefore, patients with primary renal magnesium wasting should be tested for *HNF1B* mutations to ensure early detection and optimal management of ADTKD-HNF1B.

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Introduction

Autosomal dominant tubulointerstitial kidney disease subtype HNF1B (ADTKD-HNF1B; MIM #137920) comprises non-diabetic renal disease and maturity-onset diabetes of the young (MODY5), and it is caused by mutations in hepatocyte nuclear factor 1 homeobox beta (*HNF1B*) [1]. *HNF1B* is a transcription factor that regulates genes that are cardinal to the development of the kidney, liver, pancreas and genital tract, and its impairment consequently leads to structural and functional anomalies of these organs [1–3]. Mutations in *HNF1B* are the most frequent monogenetic cause of congenital

Fig. 1. Familial background and overview of *HNF1B* deletions. **a** Pedigrees of families F1–F3. Filled symbols represent the affected index patients. **b** Localization and size of the *HNF1B*

deletions on locus q12, chromosome 17, are shown in black. The *HNF1B* gene is situated in the highlighted area. RI = Renal insufficiency; MI = myocardial infarction.

anomalies of the kidneys and urinary tract (CAKUT) and are observed in 10–30% of CAKUT patients in the prenatal period [4]. Importantly, diagnosing *HNF1B* mutations in the clinic is difficult due to high phenotypic variability between patients, incomplete penetrance, complicated detection of heterozygous gene deletions by sequencing and a high de novo mutation rate [2].

Initial reports show that hypomagnesemia is encountered in $\pm 50\%$ of ADTKD-*HNF1B* patients and has a high specificity for *HNF1B* status [1]. Defects in *HNF1B* primarily affect renal Mg^{2+} handling in the distal convoluted tubule, where transcellular Mg^{2+} transport determines the final urinary Mg^{2+} excretion [5]. In the distal convoluted tubule, Mg^{2+} reabsorption is achieved via transient receptor potential melastatin type 6 (*TRPM6*) Mg^{2+} channels and is dependent upon the voltage gradient set by the $Na^+-K^+-ATPase$. Indeed, patients with mutations in *FXYD2*, which encodes the γ -subunit of the $Na^+-K^+-ATPase$, suffer from hypomagnesemia and renal Mg^{2+} wasting [6]. In addition, it has been shown that *HNF1B*, together with its dimerization factor *PCBD1*, regulates the transcription of *FXYD2*, which explains why *HNF1B*

and *PCBD1* mutations result in renal Mg^{2+} wasting [3, 7]. Nevertheless, mutations or deletions of *HNF1B* are infrequently considered in patients with hypomagnesemia without additional symptoms, such as diabetes or kidney abnormalities.

Here, we aim to establish hypomagnesemia as an important indicator to test for *HNF1B* mutations. We present 3 patients in whom hypomagnesemia was the first clinical manifestation of ADTKD-*HNF1B* and provide an overview of the current literature on hypomagnesemia in ADTKD-*HNF1B* patients.

Case Report

We report 3 patients diagnosed with ADTKD-*HNF1B* who presented with marked unexplained hypomagnesemia.

Patient 1 (fig. 1a, F1.II.1), a 44-year-old male of Turkish origin was found to have pronounced hypomagnesemia (0.28 mmol/l) and mild renal insufficiency (RI) during examination of his kidney stones (table 1). Urinary analysis indicated high fractional excretion of magnesium (table 1). Ultrasound showed nephrolithiasis without structural kidney abnormalities. Patient DNA was sent in

Table 1. Clinical characteristics of ADTKD-HNF1B patients

Parameter	Patient 1 (male, n = 44)	Patient 2 (male, n = 42)	Patient 3 (male, n = 33)	Reference values
Serum indices				
Na ⁺ , mEq/l	139	139	140	135–145
K ⁺ , mEq/l	3.7	3.9	3.9	3.5–5.0
Mg ²⁺ , mEq/l	0.56*	0.84*	0.86*	1.3–2.1
Ca ²⁺ , mg/dl	8.8	9.4	10.0	8.2–10.2
PO ₄ ³⁻ , mg/dl	2.7	3.3	3.1	2.3–4.7
HCO ₃ ⁻ , mEq/l	29.0	26.0	28.3	22.0–29.0
Creatinine, mg/dl	0.96	1.02	1.44*	0.6–1.2
GFR, ml/min/1.73 m ²	63*	81*	57*	>90
Uric acid, mg/dl	–	7.95	8.24*	4.0–8.0
Fasting glucose, mg/dl	400*	189*	149*	70–110
HbA1c, % of total	11.9*	9.0*	6.8	4.0–7.0
Urinary indices				
Mg ²⁺ , mmol/24 h	1.95*	1.6*	3.8*	<1.0
FEMg, %	18.9*	5.2*	11.3*	<4.0
Ca ²⁺ /creatinine, mmol/l	–	0.14*	0.04*	0.2–0.6

The fractional excretion of Mg²⁺ (FEMg) was calculated using the following formula: $\text{FEMg (\%)} = (\text{U}_{\text{Mg}} \times \text{P}_{\text{Cr}}) / ((0.7 \times \text{P}_{\text{Mg}}) \times \text{U}_{\text{Cr}}) \times 100$. GFR was derived from the Modification of Diet in Renal Disease formula.

Conversion factors for units: serum Mg²⁺ in mEq/l to mmol/l, $\times 0.5$; serum Ca²⁺ in mg/dl to mmol/l, $\times 0.25$; serum PO₄³⁻ in mg/dl to mmol/l, $\times 0.323$; serum creatinine in mg/dl to $\mu\text{mol/l}$, $\times 88.4$; serum uric acid mg/dl to mmol/l, $\times 59.485$; serum fasting glucose in mg/dl to mmol/l, $\times 0.0555$; HbA1c in % of total to mmol/mol, $\times 10.9$ –23.5. * Abnormal value.

for exome sequencing (informed consent was given for this procedure), but despite good coverage (>99%), no mutations were identified in the genes known to cause hypomagnesemia. Copy number variation analysis on the exome sequencing data revealed a 17q12 deletion (fig. 1b, Chr17:34,326,941–36,152,187, hg19), which includes the *HNF1B* gene. Heterozygous *HNF1B* deletion was confirmed by multiplex ligation-dependent probe amplification (MLPA). The deletion of *HNF1B* was not encountered in the 3 unaffected brothers (fig. 1a, F1.II.1, F1.II.3, F1.II.4) of the patient. Additional testing in the index patient (2 years later) showed diabetes mellitus, evidenced by elevated fasting glucose and glycated hemoglobin A1c (HbA1c) levels (table 1). CT confirmed the absence of kidney structural abnormalities (table 1).

Patient 2 (fig. 1a, F2.II.2), a 42-year-old French male, was referred to a nephrologist for diagnostic evaluation of symptomatic hypomagnesemia (0.42 mmol/l), discovered during the work-up of his chondrocalcinosis. Additionally, hypocalciuria, hyperglycemia, high HbA1c and hyperuricemia were observed, with renal magnesium wasting, indicating renal etiology (table 1). Ultrasound and CT of the kidneys excluded nephrolithiasis, nephrocalcinosis, cysts or other structural abnormalities. Exome sequencing yielded a heterozygous *TRPM6* variant (c.5517del, pLys1839fs). Genetic analysis of the relatives showed the presence of this *TRPM6* variant in the unaffected father (fig. 1a, F2.I.1) and sister (fig. 1a, F2.II.2). Given the recessive nature of *TRPM6*-associated disease, the *TRPM6* p.Lys1839fs variant was ruled out as the cause of hypomagnesemia. Successive *HNF1B* MLPA testing in the patient confirmed a heterozygous *HNF1B* deletion (fig. 1b, Chr17:34,619,998–36,152,274, hg19).

Patient 3 (fig. 1a, F3.II.3), a 32-year-old Dutch male, was referred for further analysis of unexplained hypomagnesemia (0.43

mmol/l) with renal magnesium wasting (table 1). Hypomagnesemia (0.21 mmol/l) was discovered by chance during intensive care admission for a pulmonary embolism in 2004. In addition, the patient had hypocalciuria and a mild RI without proteinuria (table 1). Ultrasound showed 2 cysts in the right kidney (1.5 and 1.3 cm) and 1 cyst in the left kidney (1 cm). The patient's history included failure to thrive as a child, epilepsy and mental retardation. Copy number variation analysis of the exome sequencing data yielded a 17q12 deletion (fig. 1b, Chr17:34,431,920–36,214,800, hg19) that included *HNF1B* as confirmed by MLPA. During follow-up, the patient developed diabetes mellitus for which insulin was started.

Discussion

This case series reports 3 patients with *HNF1B* mutations in whom hypomagnesemia was the initial and predominant symptom of the disease. In contrast to the suggestion that hypomagnesemia is a late manifestation of ADTKD-HNF1B, our findings indicate that impairment of renal Mg²⁺ handling can arise when no impairment of kidney function or diabetes mellitus is present [8]. Timely detection of *HNF1B* mutations will enable better disease management, which includes treatment of MODY5, electrolyte disturbances, genetic counseling, gynecological examination for uterine abnormalities and follow-up

Table 2. Literature overview of hypomagnesemia in ADTKD-HNF1B patients

Research article	Patient inclusion criteria	Adults with hypomagnesemia (percentage)	Children with hypomagnesemia (percentage)
Adalat et al., 2009 [1]	Children with renal cysts and diabetes mellitus; undiagnosed renal cystic disease; or index patients with kidney malformations and a family history of renal disease, diabetes mellitus or gout	–	8/18 (44)
Faguer et al., 2011 [12]	Patients older than 16 with renal disease with multisystem involvement (diabetes with a MODY phenotype, pancreatic hypoplasia, unexplained elevated liver enzymes or genital tract abnormalities) and/or renal disease of unknown origin but concomitant findings suggestive of autosomal-dominant inheritance and/or unexplained renal disease presenting with hypodysplasia and renal cysts and/or family screening in first-degree relatives of <i>HNF1B</i> mutation carriers	10/16 (63)	–
Raaijmakers et al., 2015 [8]	CAKUT patients from the pediatric and adult nephrology department from January 2010 until April 2013, having at least one major renal anomaly (fetal bilateral hyperechogenic kidneys, multicystic dysplastic kidney, renal agenesis, hypoplastic or dysplastic kidneys, cysts of unknown origin) or one minor renal anomaly (ectopic kidney, vesicoureteral reflux, hydronephrosis) combined with one or more extra-renal anomalies associated with <i>HNF1B</i> mutations in the personal history or a familial history of renal or extra-renal manifestations	4/7 (58)	1/13 (8)
Heidet et al., 2010 [11]	Unrelated subjects with one of the following features: hyperechogenic kidneys with a size ≤ 3 SD; multicystic kidney disease; renal agenesis; renal hypoplasia; cystic dysplasia; or hyperuricemic tubulointerstitial nephropathy not associated with a <i>UMOD</i> mutation	Not quantified	Not quantified
Faguer et al., 2014 [2]	The cohort was comprised of 433 consecutive patients tested for <i>HNF1B</i> between January 2008 and June 2011 in Toulouse. Only probands presenting with features suggestive of <i>HNF1B</i> -related disease were included, whereas relatives tested for family screening were excluded	3/17 (18)	0/39 (0)
Clissold et al., 2015 [14]	Probands with renal disease referred for <i>HNF1B</i> genetic testing to Exeter Molecular Genetics Laboratory from 1998 to 2012 were included, with renal structural anomalies not due to other recognized causes (including antenatal renal abnormalities, hyperechogenicity, cysts, hypoplasia, multicystic dysplastic kidney, urinary tract malformations, solitary kidney and glomerular cysts/oligomeganephronia on biopsy), young-onset diabetes, pancreatic hypoplasia or evidence of pancreatic exocrine failure, a positive family history of either renal disease or diabetes in parent/child, genital tract malformations, liver test abnormalities of unknown etiology, hypomagnesaemia and early-onset gout	8/61 (12.1)	3/117 (2.6)

It should be noted that in many cohorts the patients were not included based on predefined selection criteria, but were selected for *HNF1B* testing by physicians for various reasons.

of anomalies that might manifest later in the course of the disease [8–10].

Since the first reported association of hypomagnesemia with *HNF1B* mutations in 2009 [1], several articles have found that hypomagnesemia is frequently encountered in patients with ADTKD-HNF1B [2, 8, 11, 12]. In

table 2, all studies with ADTKD-HNF1B cohorts reporting hypomagnesaemia are listed. This overview of the occurrence of hypomagnesemia in patients with *HNF1B* mutations demonstrates the discrepancy between studies systematically assessing Mg^{2+} status and studies based on retrospective patient file analysis. In studies that have

systematically tested serum Mg^{2+} concentrations, the prevalence of hypomagnesemia in ADTKD-HNF1B patients ranges between 25 and 75%, depending on the cohort [1, 8, 12]. Pediatric cohorts tend to show a slightly lower prevalence of hypomagnesemia (table 2). Interestingly, studies in which hypomagnesemia is part of retrospective analysis report prevalence between 3 and 10%. This difference may be explained by the use of the entire cohort as a denominator in these studies, whereas Mg^{2+} determinations are not part of routine measurements and were not performed in many cases.

In general, the prevalence of hypomagnesemia and other electrolyte disorders in ADTKD-HNF1B may be higher than previously reported. Epidemiological data regarding the clinical characteristics of ADTKD-HNF1B are predominantly derived from pre-selected CAKUT cohorts [2, 8, 13, 14]. Hypomagnesemia may be an important predictor of *HNF1B* mutations, which are accountable for approximately 10% of kidney abnormalities in all CAKUT patients [8, 11]. Systematic testing of Mg^{2+} status is still not routinely performed in CAKUT cohorts. Moreover, no large-scale data are available of ADTKD-HNF1B patients who were initially diagnosed with other symptoms, like diabetes mellitus. Consequently, this selection bias might overestimate the occurrence of structural kidney defects and underestimate the associated electrolyte disorders, including hypomagnesemia. Therefore, current clinical guidelines to select patients for genetic *HNF1B* testing may be largely dependent on kidney abnormalities, and clinicians may be reluctant to test patients with isolated hypomagnesemia for *HNF1B* deletions and mutations.

Recently, a *HNF1B* score has been developed as a diagnostic tool to select patients for *HNF1B* analysis [2]. However, only 1 patient of all the cases presented in this paper would have met the threshold criteria of the *HNF1B* score, mainly due to the absence of structural kidney abnormalities in the other 2 patients [2]. The ADTKD-HNF1B cases, from which the *HNF1B* score has been derived, were selected until 2010, which is shortly after hypomagnesemia was first reported in these patients. Additionally, the score is based on retrospective analysis. In many of the cohorts that were implemented in the *HNF1B* score Mg^{2+} status was not assessed, and consequently, hypomagnesemia was found in only 4% of the patients [2]. As a result, hypomagnesemia is underappreciated as an indicator for *HNF1B* mutations in the *HNF1B* score, as has been noted by follow-up reports [8]. Moreover, *HNF1B* deletions are often part of a 17q12 microdeletion syndrome, as in our patients, Mg^{2+} status was only measured in a paucity of patients with 17q12 deletions [15–17]. These findings em-

phasize the lack of regular Mg^{2+} measurements, even in patients with *HNF1B* deletions. Additionally, hypomagnesemia patients are not routinely tested for large deletions, and these deletions are easily missed by sequencing.

In this case series, ADTKD-HNF1B patients were diagnosed after evaluation of their isolated hypomagnesemia, without diabetes mellitus or structural kidney abnormalities. As illustrated by these cases, *HNF1B* deletions are often not identified by sequencing, but become apparent only after successive analyses such as MLPA. Mutations in *HNF1B* are among the most common genetic causes of hypomagnesemia. Nevertheless, *HNF1B* mutations are generally only diagnosed when patients develop diabetes mellitus or when structural kidney defects are identified. Therefore, we propose that patients with primary hypomagnesemia should be tested for *HNF1B* mutations, even in the absence of renal cysts or diabetes, to diagnose ADTKD-HNF1B at an early stage and enable optimal management of the disease. Moreover, Mg^{2+} concentrations should be systematically assessed in CAKUT patients, since it strongly predicts *HNF1B* mutations. Earlier detection of *HNF1B* mutations in patients with primary hypomagnesemia will result in a better management of the disease.

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Disclosure Statement

The authors have no conflict of interest to declare.

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