Familial Hypomagnesaemia with Hypercalciuria and Nephrocalcinosis: The First Four Patients in Serbia

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SUMMARY

Introduction Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive disease characterized by excessive renal magnesium and calcium wasting, bilateral nehrocalcinosis and progressive renal failure. This is the first report of FHHNC of four patients in Serbia.

Outline of Cases The first three patients were siblings from the same family. The index case, a 9-year-old girl, presented with severe growth retardation, polyuria and polydipsia, while her brothers, 11 and 7 years old, were disclosed during family member screening. The father had a urolithiasis when aged 18 years, while intermittent microhaematuria and bilateral microlithiasis persisted later on. The fourth patient, a 16-year-old boy with sporadic FHHNC was discovered to have increased proteinuria at routine examination of urine before registration for secondary school. He was well grown up, normotensive, but had moderate renal failure (CKD 3 stage), mild hypomagnesaemia and severe hypercalciuria and nephrocalcinosis. Beside typical clinical and biochemical data, the diagnosis of FHHNC was confirmed by mutation analysis of the CLDN16 gene; in all four affected individuals a homozygous CLDN16 mutation (Leu151Phe) was found. Treatment with magnesium supplementation resulted in the normalization of serum magnesium levels only in one patient (patient 4), but hypercalciuria persisted and renal failure progressed in all patients.

Conclusion FHHNC is a rare cause of chronic renal failure. The first four patients with FHHNC in Serbia have been here described. The diagnosis of FHNNC based on the findings of nephrocalcinosis with hypomagnesiaemia and hypercalciuria, was confirmed by homozygous paracellin1-mutation exhibiting a Leu151Phe.

Keywords: CLDN16; paracellin-1 mutation; medullary nephrocalcinosis; chronic renal failure

INTRODUCTION

Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC, OMIM #248250) is a rare autosomal recessive disease characterized by excessive renal magnesium and calcium wasting, bilateral nehrocalcinosis and progressive renal failure [1-6]. A primary defect of FHHNC is the impairment of the reabsorption of magnesium and calcium in the medullary thick ascending limb of the loop of Henle of the kidney (TAL) [6-10]. The clinical course of the disease is highly variable, as well as the progression rate of renal failure [5]. Mutations in Claudin 16 (CLDN16), previously known as paracellin-1, were identified as the underlying genetic defects of FHHNC [6-10]. Treatment consisting of magnesium salts, potassium citrate and thiazides seems to have no effect on the progression of renal failure in this severe disease [7-12].

Up to now, FHHNC has not been reported in Serbia. This is the first report of FHHNC in four patients in Serbia. The first three patients were siblings from the same family, while the remaining patient was a sporadic case.

CASE REPORTS

Patients and methods

Patient 1 was a girl aged 9 years at the time of the diagnosis of FHHNC. She was born as the second child after uneventful pregnancy. The delivery was normal, as well as her birth length and weight (54 cm and 2500 g, respectively). From early childhood she had polydipsia. At the age of 3 years she underwent endocrinological examinations due to growth retardation, but the cause of the growth retardation remained unclear. During reevaluation 6 years later, abdominal ultrasound was performed which disclosed medullary nephrocalcinosis. Further examinations done by paediatric nephrologists revealed a 9-year severe growth retarded girl [body height (BH) 119 cm; score of standard deviation for height (SDS) -2.75, with normal blood pressure (BP), without oedema, mild dehydration with chronic kidney disease stage 2 (creatinine clearance of 66.5 ml/min/1.73 m^2) associated with hypomagnesiemia, hypercalciuria, increased urinary fractional excretion of magnesium and sterile pyuria]. She had also a mild mental retardation, and during follow-up she exhibited hearing impairment. The parents come from the same village in the South of Serbia but are not knowingly related; the father had a urolithiasis when aged 18 years, while intermittent microhematuria and bilateral microlithiasis persisted later on.

The next two patients (patients 2 and 3) were brothers of the patient 1. They were 11 and 7 years old when the diagnosis of FHHNC was disclosed during family member screening (Figure 1). They had been generally well but clinical evaluations revealed a history of poly-

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Table 1. Clinical characteristics of the patients

Patient	Sex	Age at Dg (years)	Follow-up (years)	Poliuria/ polidipsia	Nephro-calcinosis	Muscular cramps	Extrarenal impairment	Body height (cm)		SDS at Dg	Blood pressure (mm Hg)	
								Dg	End		Dg	End
1	F	9	3.5	+/+	+	+	Psychomotor retardation, hearing impairment	115	140	-2.75	90/60	110/70
2	M	11	3.5	+/+	+	+	-	140	162	-0.2	100/60	130/95
3	M	7	3.5	+/+	+	+	-	111	129	-1.7	100/60	100/60
4	M	16	1.5	+/+	+	-	-	175	183	-	120/80	110/70

F – female; M – male; Dg – at diagnosis; End – at the end of follow-up

Table 2. Biochemical findings at the time of diagnosis (Dg) and at the end of follow-up (End)

Patient	Serum magnesium (mmol/l)		Fractional excretion of magnesium in urine (%)		Serum calcium, phosphate, bicarbonate, alkaline phosphatase		Serum creatinine (μmol/l)		Clearance (ml/min/1,73 m^2)		Parathormone (pg/ml)		Urinary calcium/ creatinine (mg/mg)		Urinary protein/ creatinine (mg/mg)	
	Dg	End	Dg	End	Dg	End	Dg	End	Dg	End	Dg	End	Dg	End	Dg	End
1	0.43	0.50	19.8	24.8	Normal	Normal	87	112	66.5	33.48	34.2	140	0.3	0.89	0.53	0.24
2	0.52	0.39	9.6	14.66	Normal	Normal	85	132	80.1	55.04	28.9	/	0.48	0.45	0.42	0.77
3	0.62	0.56	12.1	14.67	Normal	Normal	73	115	74.5	42.84	31.6	78	0.63	0.64	0..5	0.44
4	0.56	0.81	24.1	16.49	Normal	Normal	175	252	41.6	32.11	219.7	198.4	4.05	0.91	4,93	0.54

uria/polydipsia, unexplained abdominal pains and muscular spasms. Their clinical and laboratory findings are presented in Tables 1, 2 and 3, while abdominal plain radiographs showing nephrocalcinosis are documented in Figures 2 and 3.

The remaining patient (patient 4) was 16 years old when, at routine examination of urine before registration for secondary school, trace of proteinuria was discovered. Further examination showed medullar nephrocalcinosis of the right kidney (diameter 81 mm) and calcification of the cortical parenchyma of the left kidney (diameter 71 mm), decreased creatinine clearance (41.6 ml/min/1.73 m^2), hypomagnesaemia and hypercalciuria. His physical findings were normal. Family history was unremarkable.

Follow-up of the patients

Follow-up of the patients ranged from 1.5 to 3.5 (mean 2.65) years. The treatment included magnesium supplements, potassium citrate, and when needed vitamin D cholecalciferol, a recombinant growth hormone (patient 1 from the beginning and patient 3 when SDS decreased to <2), and antihypertensive therapy (in patient 3). Serum magnesium normalized only in the patient 4, while in others it remained rather low due to irregular therapy. Hypercalciuria persisted in all patients and chronic renal failure significantly progressed (66.88±7.45 vs. 48.87±5.29 ml/min/1.73 m^2; $p<0.05$).

Table 3. Complications

Complications	Patient			
	1	2	3	4
Muscular cramps	+	+	+	-
Cerebral convulsions	-	-	-	-
Proteinuria	+	+	+	+
Arterial hypertension	-	-	+	-
Anaemia	-	-	-	-
Secondary hyperparathyreoidism	-	-	-	+
Chronic renal failure	+	+	+	+

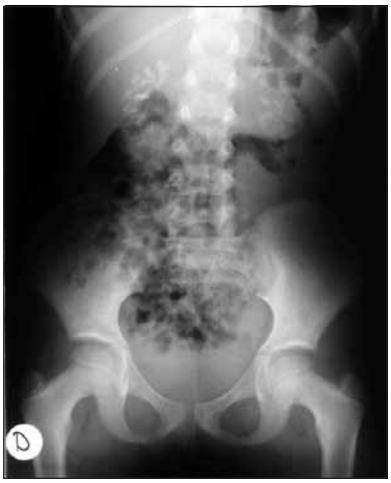

Figure 1. Native abdominal radiography in patient No 1

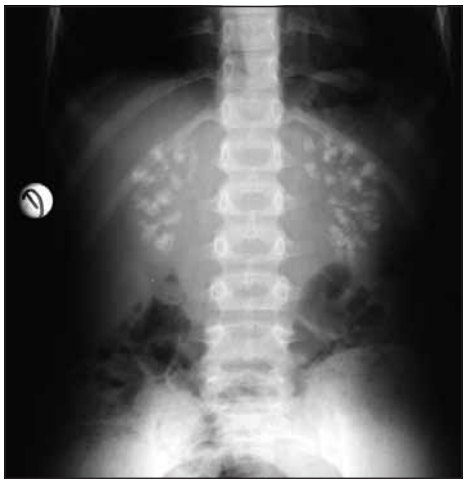

Figure 2. Native abdominal radiography in patient No 2

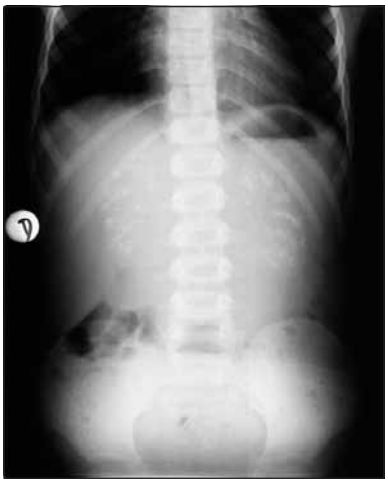

Figure 3. Native abdominal radiography in patient No 3

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Mutational analysis

Analysis of the CLDN16 gene by direct sequencing of both strands revealed a homozygous mutation (Leu151Phe) in all affected patients (for methods see ref 7 and 9).

DISCUSSION

FHHNC has not been reported in Serbia up to now. The reason might be the scarce occurrence of FHHNC, as well as the ignorance of magnesium tubular disorders. From the first report by Michelis et al. in 1972 [1] more than 60 patients were described, mostly as individual cases, or small series of patients [2, 4, 6, 7, 10, 11, 12]. Herein, we report the first four patients with FHHNC in Serbia; the first three patients were from the same family (a sister and two brothers), while the remaining patient was a sporadic case of the disease. All of our patients exhibited typical clinical, biochemical and genetic characteristics of FHHNC.

The characteristic triad included in the name of the disease is hypomagnesiemia, hypercalciuria and nephrocalcinosis. Magnesium is the second most abundant intracellular cation that participates in many enzymatic reactions as a cofactor. Its extracellular concentrations depend on the balance between intestinal absorption and renal excretion, and are maintained at near constant values under normal conditions. In the kidney, approximately 80% of total serum magnesium is filtered at the glomeruli, and more than 95% of filtered magnesium is reabsorbed along the nephron (15-20% in the proximal tubule, 65-75% in the thick ascending limb – TAL, and 5-10% in the distal convoluted tubule) [13, 14, 15]. Magnesium absorption in the TAL is paracellular (between cells) depending on electrochemical ion gradients and transmembrane voltage, while in the distal convoluted tubule it occurs via an active transcellular transport. The primary barrier to the diffusion of solutes through the paracellular pathway is provided by tight junctions (TJ) which are specialized cell-cell contacts that create an ion-selective barrier between the apical and basolateral extracellular compartments. The integral membrane proteins of TJs include occludin and claudins. The claudin superfamily of transmembrane proteins constitutes essential TJ components that either facilitate or restrict the paracellular diffusion of selective ions. The paracellular reabsorption of Mg^{2+} in the TAL is highly dependent on the transepithelial potential as a driving force [16]. The potential is generated by the electrogenic NaCl reabsorption resulting in tubular fluid dilution and the development of a lumen-positive transepithelial diffusion potential which is the driving force for Mg^{2+} reabsorption. Both claudins 16 (CLDN16) and 19 (CLDN19) contribute to the cation selectivity of tight junctions. CLDN16 functions as a Na^+ channel, whereas CLDN19 functions as a Cl^- blocker [17]. The crucial role of CLDN16 for human magnesium homeostasis is underlined by the identification of mutations in the CLDN16 of patients suffering from FHHNC [8]. The loss of CLDN16 function causes TJs to lose the cation selectivity, leading to the dissipation of the lumen-positive potential with concomitant loss of the driving force for magnesium ions reabsorption. Other tight junction proteins have also been implicated in FHHNC. Recently, mutations in claudin 19 (CLDN19) have been demonstrated in several families with the classical renal phenotype of FHHNC [18]. However the affected members of these families also had severe visual impairment consistent with the expression of this tight-junction protein not only in the kidney but also in the retina.

The defect in renal magnesium handling in FHHNC is associated with high urinary excretion rates of calcium. This might be explained by the fact that calcium and magnesium transport systems in the kidney are frequently linked, which has also been demonstrated for the paracellular pathway of both divalent cations in the TAL. However, serum calcium levels in FHHNC patients remain within the normal range, but a tendency toward hypocalcemia is also known in FHHNC [19]. In FHHNC hypocalcaemia seems to be prevented by alternative pathways in calcium homeostasis: transcellular tubular calcium reabsorption in the distal convoluted tubules, intestinal calcium absorption and calcium release out of the bone substance mediated by different hormones, such as 1.25-$(OH)_2$-cholecalciferol and parathyroid hormone. On the other hand, persistent hypercalciuria seems to play an important role in FHHNC pathophysiologic processes contributing to the development of nephrocalcinosis and renal stone formation.

The clinical manifestations of FHHNC are usually presented in early childhood by recurrent urinary tract infections, polyuria, polydipsia, and growth retardation [9]. Some of the patients suffer of nephrolithiasis, cerebral convulsions, muscular tetany, or abdominal pain. In our patients main symptoms were polyuria, polydipsia, muscular cramps, abdominal pain and growth retardation. Growth failure is a prevalent clinical manifestation of FHHNC, as described by Haffner et al. [20] and other authors [5, 10]. It is explained on the basis of hypocalcemia, hypomagnesiaemia and urine concentration defects. The majority of the patients have renal failure at the time of the diagnosis, and almost one third of the patients reach end stage renal failure already during adolescence requiring renal replacement therapy. Praga et al. [6] reported that six of eight patients required chronic dialysis after 1-7 years. Weber et al. [7] reported a median age for end-stage renal failure of 14.5 years (range 5.5-37.5 years). The variable development of terminal renal failure in FHHNC may be determined by the degree of calciuria, nephrocalcinosis, and the type of mutation, gender, or ethnic differences. However, recently, Konrad et al. [21] reported that genetic background has a major impact on the progression of renal failure; the 23 patients who had mutations resulting in complete loss of function of both alleles were significantly younger at the onset of symptoms than the 46 patients who had at least one mutant allele providing partial function (2.2 versus 5.6 years; $p<0.01$). In addition, those with complete loss of function had a more rapid decline in glomerular filtration rate (7.3 versus 2.9 ml/min per 1.72 m^2/y; $p<0.01$), leading to 54% requiring renal replacement therapy by age 15 compared with 20% of those with residual function ($p<0.05$). These data suggest that the residual function of claudin-16 may delay the progression of renal failure in FHHNC [21].

FHHNC is a progressive tubulointerstitial disease which advances from nephrocalcinosis to tubulointerstitial fibrosis and glomerulosclerosis. However, nephrocalcinosis cannot fully explain the progressive nature of FHHNC. Ikenouchi et al. [22] have demonstrated that epithelial-to-mesenchymal transformation, which plays a major role in the progression of renal fibrosis, is associated with down regulation of claudins and occludin, major proteins of the tight junction complex. It has been speculated that defective claudin-16 function could be an early event in disruption of the tubular tight junction complex, followed by alterations of cell polarity and an induction of tubular dysplasia [21]. Therefore, tubular dysplasia might be a key event of the progression of FHHNC.

Defective claudins may be also involved in other tissue than renal causing extrarenal abnormalities. The most common of them include ophtalmological complication (such as severe myopia, nystagmus, chorioretinitis and macular coloboma) [6], hair loss [11], hearing impairment [4] and dental abnormalities [23], but severe multiple malformations are exceptionally rare [24]. Only one of our patients (patient 1) exhibited extrarenal abnormalities in the form of mild mental impairment and hearing defect.

The diagnosis of FHNNC is based mainly on the findings of hypomagnesaemia with hypercalciuria. In cases of hypercalciuria and hypomagnesaemia, other disorders, such as distal renal tubular acidosis [3], familial isolated hypomagnesaemia [25], familial hypomagnesaemia with hypokalemia (Gitelman syndrome) [26], drug side-effects or occasionally "classic" Bartter syndrome, [27], must be taken into consideration. During the progression of chronic renal failure hypomagnesaemia is decreasing, and when normalized in uremic patients, it is difficult for the diagnosis of FHHNC. The additional biochemical findings in FHHNC are an increased parathyroid hormone (PTH) that is not in correlation with the degree of renal impairment, incomplete renal tubular acidosis, hyperuricosuria, and decreased urinary citrate excretion. Increased PTH levels before chronic renal failure may be explained by the excessive loss of calcium with subsequent mobilization from bone and stimulatory effect of hypomagnesaemia on PTH secretion.

Finally, the diagnosis of FHHNC is confirmed by genetic analysis by disclosing mutation mainly in CLDN16. Also, genotyping in patients with FHHNC will allow the prediction of the clinical course to some extent and improve genetic counselling of affected families [21]. From the first molecular genetics study by Simon et al. in 1999 [8], more than 30 different mutations have been identified [5, 7, 28, 29, 30], but most of them (almost 75%) affect the first and second extracellular loop of the paracellin-1 molecule. The first extracellular segment is highly variable and the most common mutations from the patients from Germany and Eastern Europe exhibited a common mutation which makes easy genetic diagnosis of FHHNC in this area [7]. DNA study of our FHHNC patients revealed a Leu151Phe exchange as the causative CLDN16 mutation. This is by far the most frequent mutation due to a founder effect. Although, FHHNC is autosomal recessive, some of family members of the FHHNC patients exhibited nephrolithiasis due to hypercalciuria [6]. As supported by the results of linkage and mutational analysis, family members with hypercalciuria and/or nephrolithiasis seemed to be symptomatic heterozygotes.

The management of FHHNC is dominantly symptomatic based on the correction of hypomagnesaemia by the supplement of magnesium salts, decreasing hypercalciuria and nephrocalcinosis by potassium citrate, increased water intake, reduced intake of salt and thiazide diuretics. In addition, recurrent urinary tract infections need to be prevented, and supportive therapy of chronic renal failure should be commenced in time. Early treatment with vitamin D and calcium is essential to maintain growth. Patients with terminal renal failure are treated by renal replacement therapy. FHHNC does not recur in the transplant kidney.

Medical treatment does not appear to influence the progression of the disease. Despite magnesium substitution, normal values of serum magnesium could not be achieved in all of the patients. Three of our patients, siblings with FHHNC, had not regularly received magnesium supplement therapy, and their serum magnesium concentrations largely varied, but never normalized. In contrast, in the remaining patient (patient 4) the serum magnesium levels reached normal values due to the regularly magnesium supplementation and progression of renal failure.

In the report we describ the first four patients with FHHNC in Serbia. The main phenotypic characteristics were muscular cramps in the first three patients, growth retardation in the first and third one, while the fourth patient was free of symptoms. At the time of the diagnosis all patients had decreased renal function which progressed during further follow-up. All patients shared the same genetic CLDN16 defect (L151F).

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Фамилијарна хипомагнезијемија с хиперкалциуријом и нефрокалцинозом: прва четири болесника у Србији

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КРАТАК САДРЖАЈ

Увод Фамилијарна хипомагнезијемија с хиперкалциуријом и нефрокалцинозом (енгл. *familial hypomagnesaemia with hypercalciuria and nephrocalcinosis – FHHNC*) је редак, аутозомно рецесивно наследан синдром који се одликује великим губитком магнезијума и калцијума урином, обостраном нефрокалцинозом и прогресивном хроничном инсуфицијенцијом бубрега (ХИБ). У овом раду дат је приказ прва четири болесника из Србије код којих је доказан *FHHNC* и преглед досадашњих сазнања о овом тешком обољењу.

Приказ болесника Три болесника су деца из исте породице. Болест је прво откривена код деветогодишње девојчице ниског раста, док је код њене браће, узраста од седам и једанаест година, дијагностикована током циљног испитивања чланова породице. Код све троје деце су доказани полиурија, полидипсија, хипомагнезијемија, повећано излучивање магнезијума и калцијума урином, медуларна нефрокалциноза и ХИБ. Консангвинитет у породици није потврђен. Отац ове деце је у својој младости патио од уролитијазе, а касније и од интермитентне микрохематурије и микролитијазе. Четврти болесник је спорадичан случај. Код њега је *FHHNC* откривен у узрасту од 16 година током испитивања узрока асимптоматске протеинурије. Тада је већ имао умерену ХИБ (трећи стадијум хроничне болести бубрега) удружену са благом хипомагнезијемијом, тешком хиперкалциуријом и обостраном нефрокалцинозом. Код свих болесника *FHHNC* је потврђен налазом хомозиготне мутације гена *CLDN16* (*Leu151Phe*). Болесници су клинички праћени у просеку 2,65 година. Примењена је супституциона терапија солима магнезијума и калијум-цитратом, а по потреби болесници су добијали рекомбинантни хормон раста, витамин Д и антихипертензивну терапију. Концентрације магнезијума у серуму су се нормализовале само код четвртог болесника. Сви болесници су имали сталну хиперкалциуријуу и умерену прогресију ХИБ.

Закључак *FHHNC* је редак узрок ХИБ. Описана су прва четири болесника са *FHHNC* у Србији. Дијагноза обољења је постављена на основу налаза нефрокалцинозе с хипомагнезијемијом и нефрокалциуријом, а потврђена хомозиготном мутацијом парацелина 1 (*Leu151Phe*).

Кључне речи: *CLDN16*; мутација парацелина 1; медуларна нефрокалциноза; хронична инсуфицијенција бубрега

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