# Familial hypomagnesemia with hypercalciuria and nephrocalcinosis – case reports and differencial diagnosis

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**Familial hypomagnesemia with hypercalciuria and nephrocalcinosis is a rare AR inherited disorder with not favourable prognosis regarding renal functions. End-stage renal disease is present in 1/3 of adolescent patients, timing of renal failure correlates with severity of nephrocalcinosis. Molecular nature of disease is based on mutations of gene encoding protein paracellin-1 (claudin-16), which is expressed in medular and cortical segment of Henle loop. This protein takes place in the structure of tight intercellular junctions which are important for paracellular transport of Mg and Ca. Nephrolithiasis has been described also in heterozygots. We refer on two unrelated cases. A 5 year-old boy with history of nephrolithiasis had findings of hypomagnesemia, hypermagnesiuria, hypercalciuria, hypocitraturia, hyperparathyreosis, slight hyperuricaemia and ultrasound of nephrocalcinosis. Renal wasting of other ions, glucose, aminoacids, proteins and oxalats was not present. Renal functions were slightly decreased, concentration ability was lowered, but without polyuria. Test of acidification excluded renal tubular acidosis. Blood pressure reached 95‰ . Other examinations were (except of slightly positive Chvostek sign) within physiologic ranges. Family history was positive for nephrolithiasis in father´s sister. Another 5 year-old boy was admitted for acute abdominal pain, abdominal X-ray revealed severe nephrocalcinosis, laboratory findings were similar as above, just somewhat milder and without hyperparathyreosis. For differencials some other hereditary magnesium-loosing renal diseases with severe hypomagnesemia should be excluded: 1. Activating mutations in Ca-Mg receptor with hypercalciuria, nephrocalcinosis and hypoparathyreosis 2. Salt loosing tubular disorders – Bartter syndrome (I-III) and Gitelman syndrome 3. Hypomagnesemia with secondary hypocalciuria and peripheral resistance to parathormone 4. Isolated hypomagnesemia – recessive without any other defect, and dominant with hypocalciuria. (NEPHROL. DIAL. POL. 2006, 10, 135-139)**

**Key words:**
- hypomagnesemia
- hypermagnesiuria
- hypercalciuria
- nephrocalcinosis
- renal failure
- differential diagnosis

## Rodzinna hipomagnezemia z hiperkalciurią i wapnicą nerek – opis przypadku i diagnostyka różnicowa

**Rodzinna hipomagnezemia z hiperkalciurią i wapnicą nerek jest rzadką chorobą dziedziczoną AR o niekorzystnym rokowaniu czynności nerek. Schyłkowa niewydolność nerek występuje u 1/3 dorosłych pacjentów, a czas niewydolności nerek koreluje ze stopniem zaawansowania wapnicy nerek. Molekularną przyczyną choroby jest mutacja genu kodującego proteinę paracellin-1 (claudin-16), której ekspresję stwierdza się w rdzeniowej i korowej części pętli Henle'go. Proteina ta współtworzy strukturę połączeń międzykomórkowych, ważnych dla okołokomórkowego transportu Mg and Ca. U heterozygot była opisywana także kamica nerek. Praca przedstawia dwa niespokrewnione przypadki kliniczne. U chłopca 5-letniego z kamicą dróg moczowych w wywiadzie stwierdzono hipomagnezemię, hipermagnezurię, hipercalciurię, hipocitraturię, hiperparatyreozę, nieznaczną hiperurikemię oraz wapnicę nerek w wywiadzie. Nie obserwowano utraty nerkowej innych jonów, glukozy, aminokwasów, białek ani szczawianów. Funkcja nerek była w niewielkim stopniu upośledzona z obniżeniem zdolności zagęszczania, bez wielomoczu. Wykluczono nerkową kwasicę cewkową w teście zakwaszania. Ciśnienie tętnicze było w zakresie 95‰. Poza lekko dodatnim objawem Chwostka, pozostałe badania były w zakresie norm fizjologicznych. Wywiad rodzinny był dodatni w kierunku kamicy nerkowej u siostry ojca dziecka. Drugi chłopiec lat 5 został skierowany do szpitala z powodu ostrego bólu brzucha – kolki nerkowej, badanie rtg jamy brzusznej wykazało znacznie nasiloną wapnicę nerek, badania laboratoryjne były podobne do wymienionych powyżej, nie stwierdzono jednak nadczynności przytarczyc ani nadciśnienia tętniczego. W diagnostyce różniowej należy wykluczyć wrodzone choroby nerek z utratą magnezu i nasiloną hipomagnezemią: 1. Mutacje receptora Ca-Mg z hipercalciurią, wapnicą nerek i**

**Słowa kluczowe:**
- hipomagnezemia
- hipermagnezemia
- hiperkalciuria
- nefrokalcynoza
- niewydolność nerek
- diagnostyka różnicowa

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**niedoczynnością przytarczyc 2. choroby cewkowe z utratą soli - zespoły Bartter'a (I-III) i Gitelman'a 3. Hipomagnezemia z wtórną hipokalciurią i opornością obwodową na parathormon 4. Izolowana hipomagnezemia - postać recesywna bez innych defektów oraz dominująca z hipokalciurią.**

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**Introduction**

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive inherited disorder with primary disturbance of tubular kidney transport of magnesium and calcium. Magnesium is a very important intracellular cation taking part in mechanism of neuromuscular excitability, in synthesis of proteins, in stability of nucleic acids and in oxidative phosphorylation. Physiologic ranges are rather narrow – 0.7-1.1 mmol/l. In normal condition – uptake and excretion of magnesium is balanced. Daily uptake of magnesium is around 6 mmol, maximum is absorbed in small intestine, little amount in colon. There are two ways of Mg intestinal absorption: 1. active transport – saturable, transcellular 2. passive transport – paracellular, dependent on electrochemical gradient. (There exists also genetic defect in Mg intestinal absorbtion – that might be a part of differential diagnosis – as we will mention later). Magnesium is eliminated by two ways: 1. Secretion to intestine – 2 mmol/day and 2. The more important – excretion by kidney – around 4 mmol/day. Excretion of Mg in kidney takes place in three main places. 1. Proximal tubule – 15-20% of reabsorbtion $Mg^{2+}$ in mature kidney; in immature kidney of newborn – 70% . 2. Loop of Henle – thick ascending limb – 70% of reabsorbtion $Mg^{2+}$; the transport is passive, paracellular. 3. Distal convoluted tubule - 5-10% of reabsorbtion $Mg^{2+}$; the transport is active, transcellular; indicates definite $Mg^{2+}$ excretion – FE 3-5% (Figure 1) [4,5].

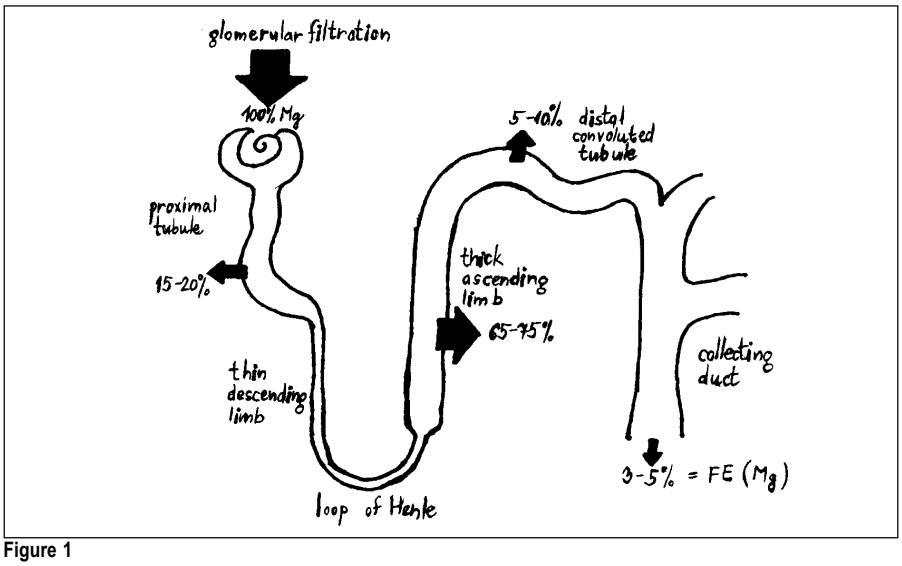


**Figure 1**
**Scheme of magnesium tubular reabsorption.**

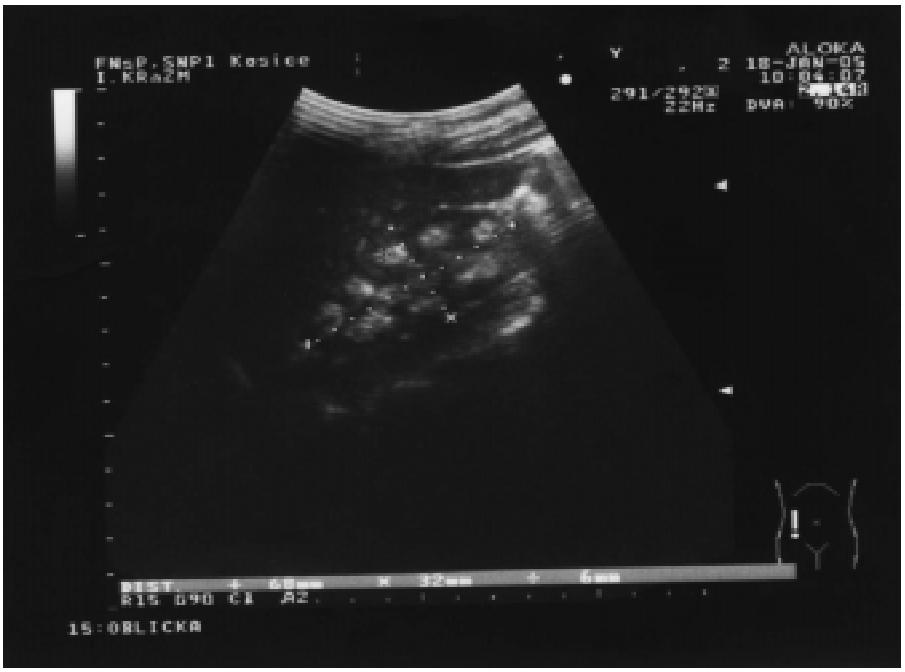


**Figure 2**
**Severe bilateral nephrocalcinosis in patient 1.**

In FHHNC, the defect is localised in Henle loop – the place of maximal Mg reabsorption. Molecular nature is based on mutations of gene encoding protein paracellin-1 (claudin-16), chromosomal locus 3q27 which is expressed in both medullar and cortical segment of Henle loop in its thick ascending limb, and partially in distal convolute tubule [11]. Paracellin 1 is a protein cosisting of 305 aminoacids with 4 transmembrane domains and two extracellular loops. This protein takes place in the structure of tight intercellular junctions which are important for paracellular transport of Mg and Ca – specifically for their flux from apical to basolateral cell surfaces. Most mutations are localized in the first extracellular loop that bridges the intercellular space - what is important for disturbing of para-cellular conductance. Many of these mutations are based on a change of Leu 151 for another aminoacid (Phe, Trp, Pro) [13]. In Middle and Eastern Europe the most abundant mutated allele (about 50%) is Leu151Phe, confirming possible founder effect [13]. The mentioned mutations are usually connected with classical phenotype of FHHNC. On the other hand, there has been described a mutation leading to a distinct clinical phenotype with much better prognosis – Thr233Arg. This change leads to the mutated protein with disabled association to another important protein – tight junction scaffolding protein Z01 – with the consequence of mutated paracellin 1 accumulation in lysosomes instead of tight junctions [8].

Clinically – initial symptoms are usually urinary tract infection, polyuria /nocturnal enuresis and hematuria or renal colic or due to nephrolithiasis/ or urolithiasis. Significant neurologic symptoms due to hypomagnesiemia are not frequent, although the patients can have higher susceptibility to neuromuscular excitability and convulsions. Sometimes also eye symptoms can be present – myopia, nystagmus, chorioretinitis. The age of the first manifestation ranges from 2 months to 18 years, with median of 3.5 years – though the age of the right diagnosis is often higher [13]. Laboratory tests reveal hypomagnesemia, hypercalciuria and high urinary excretion of magnesium – despite of marked hypomagnesemia. Secondary metabolic consequences of the disorder are hyperuricaemia, hypocitraturia, hyperparathyreosis and sometimes incomplete distal renal tubular acidosis. Imaging of kidney typically shows notable nephrocalcinosis. Disturbances of other substances excretion (mainly K, Na, bicarbonates, glucose and proteins) are not present, and

**Table I**
**Differential diagnosis of hypomagnesemia, hypercalciuria and nephrocalcinosis - a brief summary.**

| | Na (S) | Na (U) | K (S) | K (U) | Cl (S) | Cl (U) | Ca (S) | Ca (U) | Mg (S) | Mg (U) | PTH | NC | PG | acid base |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FHHNC | N | N | N | N | N | N | N ↓ | ↑ | ↓ | ↑ | ↑ | + | N | N or acidosis |
| Antenatal Bartter - I, II<br>Bartter IV + deafness | ↓ | ↑ | ↓ | ↑ | ↓ | ↑ | N | ↑ | N | N | N | + | ↑ | alkalosis |
| Bartter III classical | ↓ | ↑ | ↓ | ↑ | ↓ | ↑ | N | N (↓↑) | N (↓) | N (↑) | N | (+) | N | alkalosis |
| Gitelman | ↓ | ↑ | ↓ | ↑ | ↓ | ↑ | N | ↓ | ↓ | ↑ | N | - | N | alkalosis |
| AD isolated hypomagnesemia<br>with hypocalciuria | N | N | N | N | N | N | N | ↓ | ↓ | ↑ | N | - | N | N |
| AR isolated hypomagnesemia | N | N | N | N | N | N | N | N | ↓ | ↑ | N | - | N | N |
| AR primary intestinal hypomagnesemia<br>with secondary hypocalcaemia | N | N | N | N | N | N | ↓ | N | N (↓) | ↑ | N (↓) | - | N | N |
| AD hypoparathyreoidism<br>(Ca Mg sensing receptor) | N | N | N | N | N | N | ↓ | ↑ | ↓ | ↑ | ↓ | + | N | N or acidosis |

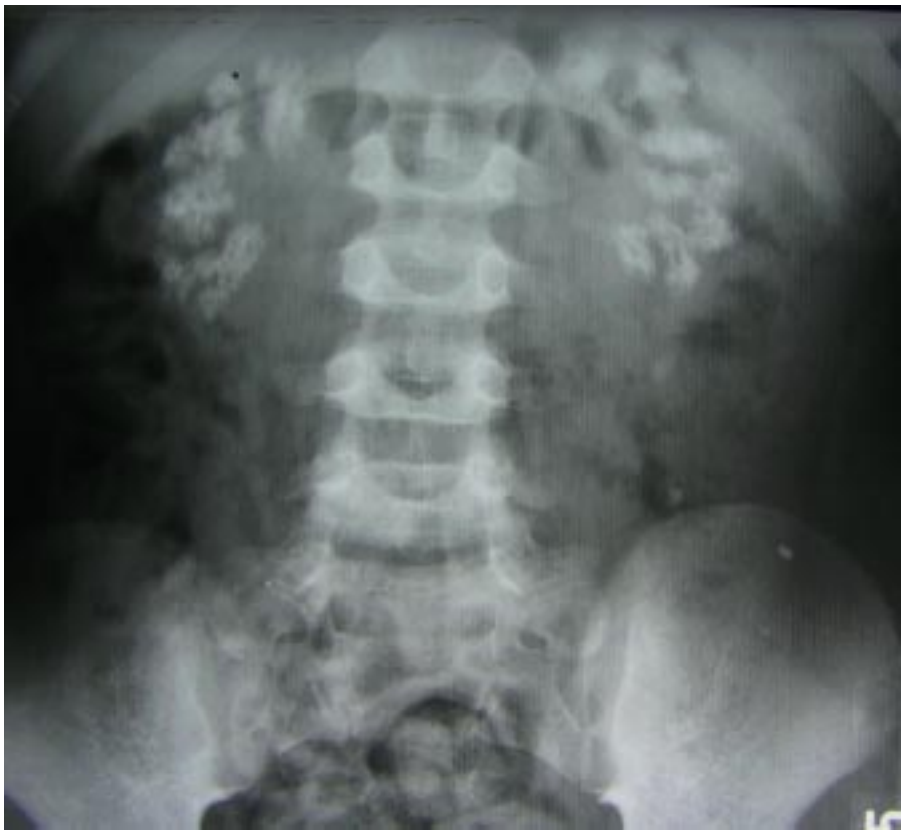

**Figure 3**
**Severe bilateral nephrocalcinosis in patient 2 - plain abdominal X-ray.**

there is no increase of stone-forming matters other than calcium (cystine, oxalates). Unfortunately, this genetic disease has not favourable prognosis regarding renal functions. End-stage renal disease is present in 1/3 adolescent pacients, timing of renal failure correlates with severity of nephrocalcinosis. However, in literature there is described a middle-aged patient with confirmed molecular diagnosis who has just mild renal failure but do not require hemodialysis/ transplantation, or cases of 3 children – sibs with nephrocalcinosis and self-limiting hypercalciuria without renal impairment [8]. Thus, it is probable that rapidity of progression might depend also on other issues - e.g. type of mutation or participation of other genes as well as external factors in pathogenesis. Heterozygots have been described to have hypercalciuria and nephro/ urolithiasis much more frequent than average population – but without nephrocalcinosis and without impairment of renal functions.

**Case reports:** We refer on two unrelated cases of boys from east Slovakia who were diagnosed in the same year. It could mean that the disease might not be as rare as it is thought and that pediatricians and pediatric nephrologists should be familiar with this diagnosis.

**Case 1:** A 5 year-old boy with a two year history of renal colic was admitted to our department for complete renal and metabolic examination. Family history was positive regarding documented ureterolithiasis of father´ s sister and one attack of pains in lumbar region typical for renal colic in proband´ s father. Otherwise the parents were healthy, nonconsanguineous, the patient has no siblings. Personal history of patient was unremarkable until his 3rd year, when he was hospitalized in a local hospital for "dark urine". Due to high uric acid he was discharged with diagnosis familial renal hyperuricaemia. Since that time he was taking Milurit (allopurinol) and magnesium due to hypomagnesemia and experienced a few times dark urine and one time renal colic with urinating of 2 small stones. Objective examination did not reveal anything notable except of constitutionally higher stature and slight obesity (121cm, 29,8 kg). Laboratory parameters discovered severe hypomagnesemia 0,34..0,40 mmol/l with hypermagnesiuria - fractional excretion (FE) of Mg 30.8%, hypercalciuria - calcium/ kreatinine 1.39, FE of Ca 5.6, hypocitraturia – 162 μmol/24 hours (our ref. values 1040-6426), hyperparathyreosis – 109 pg/ml (our ref. < 72), and slight hyperuricaemia (398 umol/l). Calcaemia was slightly lower at the beginning (Ca 2,11..2,34 mmol/l). Alkaline phosphatases were in physiologic ranges, as well as cystin and oxalates in urine; acid base was balanced. Abdominal ultrasound revealed bilateral hyperechoghenic pyramids of kidney – severe nephrocalcinosis (Figure 2). The liver was slightly enlarged and hyperechogenic – but liver enzymes were within physiologic range. Basic renal functions - glomerular filtration according to Schwarz was 59 ml/min, tubular resorption 97.1%. Renal wasting of other ions, glucose, proteins, cystin and oxalates was not present. Concentration ability was lowered, but without polyuria – maximal value in concentration test was 346 mOsm/kg urine after 5 hours. Acidification test excluded renal tubular acidosis. Blood pressure reached 95‰, 24-hour measurement confirmed diastolic hypertension; the rest of cardiologic findings were otherwise physiologic as well as other examinations (ophthalmologic, neurologic, hearing) except of slightly positive Chvostek sign. With regard to these results we estimated the diagnosis of FHHNC. Now, the patient is treated with Tritace, Hydrochlorothiazid, Milurit, magnesium; a year after diagnosis his Schwarz is 56 ml/ min, Mg 0.47..0.44 mmol/l, Ca/kreatinine 1.20..0.98, magnesiuria - FE Mg 26.1..21.9%.

**Case 2:** A 5 year old boy was admitted to a local hospital due to acute severe abdominal pain with fever, vomiting and slight

diarrhoea. Plain abdominal X-ray and ultrasound revealed bilateral nephrolithiasis/nephrocalcinosis with reduction of renal parenchyma (Picture 3). Urine was sterile, inflammation markers were just mildly increased. After symptomatic treatment the difficulties disappeared and the patient was transferred for complex evaluation to our department. Family history was positive for nephrolithiasis only in further family (proband´s mother´s father´ s sister). The parent´s relationship is not consanguineous; the younger twin sisters are healthy by now. Personal history was unremarkable, except of the statement of variable abdominal pain in last few months. Objective physical findings included pycnic habitus, perioral eczema, palpable thyroid gland and systolic hypertension sustained by 24-hour measurement. Laboratory results were not as striking as in the first patient – we found mild hypomagnesemia and hypermagnesiuria, slight hypercalciuria and hyperuricaemia (Mg 0.54, FE Mg 8.5, Ca/kreat index 1.44, uric acid 383 μmol/l). Serum calcium was 2.39 mmol/l, oxalates in urine were negative, acid base balance was within physiologic range, parathormon was also normal – 56.5 pg/ml. Ultrasound findings confirmed large foci of nephrocalcinosis in renal pyramids bilaterally (Figure 4). Basic renal function – glomerular filtration was normal (Schwarz 86 ml/min), TR 96.7% . Concentration ability was low – maximal urine osmolality after desmopresin was 327 mOsm/kg. Ophtalmologic examination revealed astigmatismus hypermetropicus. We supposed the diagnosis of FHHNC, the boy is treated with ACE inhibitor, hydrochlorothiazid and magnesium. However, later laboratory results from outpatient unit (Mg 0.54 0.76..0.66 FE Mg 11.6%.. 18.04% Ca/kreat. 1.40%) may show evidence for either lighter form of this disease or another close disorder. Both patients are planned to have DNA analysis of claudin 16 in close future.

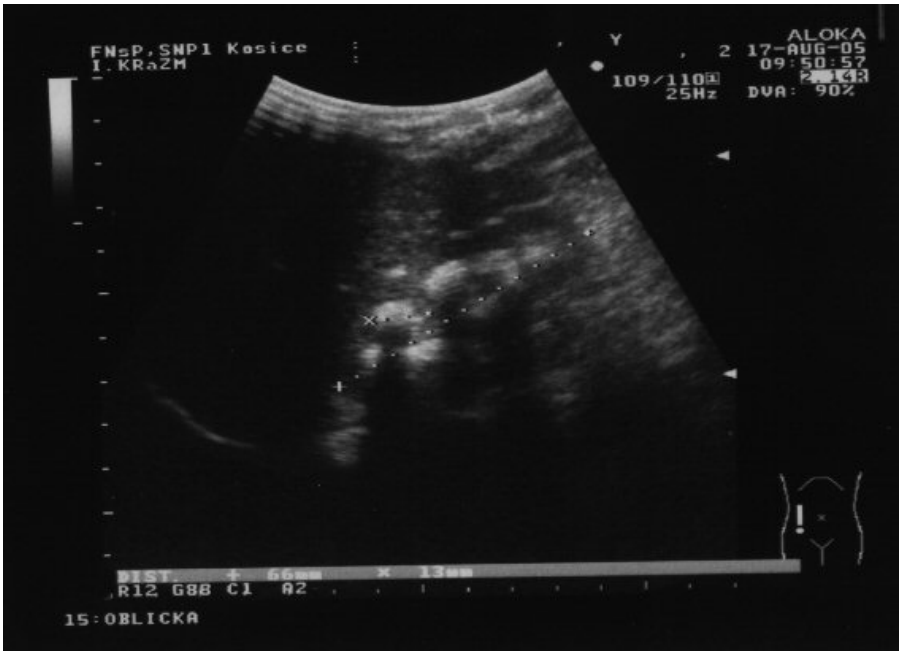


**Figure 4**
**Severe nephrocalcinosis in patient 2 – ultrasound.**

**Differential diagnosis, discussion**

The causes of hypomagnesemia can be basically divided into 3 parts:

1. Inadequate magnesium intake in diet.
2. Disturbance of magnesium intestinal absorption.
3. Magnesium wasting disorders of kidney.

Ad. 2 – Patients with severe chronic diarrhea such as Crohn disease or some other acquired disorders can suffer from hypomagnesemia from low intestinal absorption of Mg. From genetic point there should be mentioned an autosomal recessive inherited disease – primary intestinal hypomagnesemia (= hypomagnesemia with secondary hypocalciuria). The symptoms manifest in early infancy as seizures and other signs of high neuromuscular excitability and can lead to serious neurologic impairment or even death. Laboratory findings are typical of of severe hypomagnesemia with secondary hypocalcemia due to peripheral parathormone resistance. Kidneys are trying to "spare" calcium in organism what results in hypocalciuria, but renal magnesium reabsorption is still inappropriate. Molecular base is change of the gene encoding protein of ion channel TRPM6 (transient receptor potential M6) expressed in intestinal cells and distal tubule segments [10]. Hypomagnesemic hypocalcemia does not react to calcium or vitamin D, but relieves after continual magnesium administration.

Ad. 3 The group of magnesium wasting disorders of kidney where belongs also FHHNC, comprises a few subgroups.

Isolated hypomagnesemias are disorders with inappropriety high renal magnesium excretion, but without hypercalciuria or hyperexcretion of other substances. In isolated dominant hypomagnesemia the hypomagnesemia is associated only with hypocalciuria. Neurologic symptoms due to hypomagnesemia can be of various intensity – severe seizures as well as asymptomatic. The disease is caused by mutation of FXYD2 gene – gamma subunit of the Na,K-ATPase [7]. However, there have been described families with isolated dominant renal magnesium wasting that failed to link to the locus of the mentioned gene. It means that there must exist at leat one more gene responsible for the disease [3]. Isolated recessive hypomagnesemia distincts from the dominant one by the lack of hypocalciuria. Molecular base is unknown.

Salt loosing disorders – Bartter classical, or type III – hypomagnesemia is present in about 50 % of patients, calcium excretion is variable, disturbances are rather presenting as hypocalciuria. Nephrocalcinosis is NOT typically described in classical Bartter. The symptoms usually manifest in infancy or early childhood. Clinical features include polyuria, polydipsia, episodes of dehydration, salts and water depletion, later also growth retardation. Typical laboratory findings are massive NaCl wasting, hypochloremic metabolic alkalosis, hypokalemia, and high aldosteron without hypertension. Clinical severity of classical Bartter is greatly variable – ranges from severe infantile forms to slight disease diagnosed in puberty or even later. Genetic cause of disorder consists in mutations of gene for chloride channel B (CLCNKB) which is expressed in basolateral membrane of tubular epithelial cells of thick ascendent limb of Henle loop and distal convolute tubule. The channel normally mediates flux of Cl ions from the tubular cells to interstitium [6].

Salt loosing disorders – Bartter antenatal I, II – or hyperprostaglandin E syndrome – hypomagnesemia is not a typical feature; the main points for differential diagnosis are hypercalciuria and nephrocalcinosis which are present in all patients, sometimes resulting in osteopenia. Severe polyuria in utero results in polyhydramnion and premature birth (around 30 weeks of gestation), laboratory pathologies include severe salt wasting with hypokalemic metabolic alkalosis, hyperprostaglandinuria E, hyperreninemia. Clinically infants suffer from episodes of dehydration, failure to thrive, and some symptoms caused by hyperprostaglandinemia E – fever, vomiting, intermittent diarrhoea. Genetically, the syndrome can be caused by mutations of two genes (clinically undistinguishable): 1. gene for Na-K-Cl cotransporter-2 (NKCC2) – protein belonging to the solute carrier family SLC12A1 that is responsible for active NaCl reabsorption in thick ascending limb of Henle loop. 2. gene for renal outer-medullary potassium channel (ROMK1). Place of expression – from thick ascending limb of Henle loop till distal nephron. Inhibitors of prostaglandin synthesis can help to relieve some symptoms in these two disorders [5].

Salt loosing disorders – Bartter antenatal IV – with sensorineural deafness. Most severe form, similar like previous, characterised by massive loss of salt and water since birth, many times with progression to renal failure, although hypercalciuria and nephrocalcinosis are not common features. Indomethacin therapy is not successful. Genetic base is mutation of gene BSND coding protein Barttin – a beta subunit of the

renal chloride channels CLCKNB and CLCKNA and present also in K-secretoric epithelia of inner ear [2].

Salt loosing disorders – Gitelman syndrome – the mildest form of salt loosing disorders, usually diagnosed in late childhood or puberty or even later. Typical complaints are muscle weakness or tetanic spasms due to hypomagnesemia, other symptoms pose salt-craving, paresthesias, nycturia. Besides hypomagnesemia, laboratory findings include also hypocalciuria, hypokalemia and chloride-resistant metabolic alkalosis. Nephrocalcinosis is NOT a feature of Gitelman. There have been described more than 100 various causative mutations which affect SLC12A3 gene that is expressed in the distal convoluted tubule and is a part of a chlorothiazide-sensitive NaCl cotransporter [12].

Ca/Mg sensing receptor associated disorders – Ca-Mg sensing receptor (CASR) is an important link to calcium and magnesium homeostasis. CASR is located in the apical membrane of parathormon secreting parathyreoidal cells and distal nephron segments involved in Ca-Mg reabsorption [1]. Activating mutations of the CASR gene leads to increased sensitivity of receptor thus diminished PTH secretion and Ca-Mg tubular reabsorption. Clinically the patients are presented with mild to moderate hypocalcaemia, hypercalciuria and polyuria. About 50% have hypomagnesemia [9]. Vitamin D or calcium therapy are reserved just for symptomatic patients, because they dramatically increase urinary calcium excretion and may lead to nephrocalcinosis with irreversible impairment of renal function.

Mitochondrial hypomagnesemia, hypertension and hypercholesterolemia - this disorder had been recently identified in a large Caucasian family [14]. Hypomagnesemia was a consequence of renal hyper-excretion of Mg, some family members had also renal loss of potassium with hypokalemia. Clinical severity was mild. The revealed mutation lies within the mitochondrial tRNA isoleucin gene, and changes thymidine to cytidine at 4291 nucleotide.

**Summary**

FHHNC is a rare genetic disorder where the first step to diagnosis is most times uncovering of nephrocalcinosis in kidney ultrasoud due to renal infection, hematuria, or colic. Thus it is essential to think on detailed magnesium evaluation following finding of nephrocalcinosis (besides complex examination of metabolism of calcium, phosphor, natrium, potassium, chlorides, stone-forming matters, acid-base balance and others). On the contrary – it is important to order kidney ultrasound in any accidental finding of marked hypomagnesemia. In FHHNC the excretion disturbances of basic ions (Na, K, Cl) are not present. Typical findings are hypercalciuria with normo-or mild hypocalcemia and renal magnesium wasting despite serious hypomagnesemia. To other important results belong hypocitraturia, disorder of concentration capacity of kidney and hyperparathyreosis with physiologic vitamin D concentrations. Prognosis of this disease is unfavourable - end stage renal failure manifests in most patients around the 3rd decade. The treatment helps to overcome some symptoms, but does not seem to influence progression to renal failure. However, there have been described also few patients with distinct mutations of paracellin I (claudin 16) with good prognosis regarding renal function preservation. The main points for differential diagnosis are summarized in table I.

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