Familial hypomagnesemia with hypercalciuria and nephrocalcinosis – case reports and differential diagnosis

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 medullary 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, amino-acids, 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 differentials some other hereditary magnesium-losing renal diseases with severe hypomagnesemia should be excluded: 1. Activating mutations in Ca-Mg receptor with hypercalciuria, nephrocalcinosis and hyperparathyreosis 2. Salt loosing tubular disorders – Bartter syndrome (I-III) and Gitelman syndrome 3. Hypomagnesemia with secondary hyperparathyreosis and peripheral resistance to parathormone 4. Isolated hypomagnesemia – recessive without any other defect, and dominant with hypercalcuiura. (NEPHROL. DIAL. POL. 2006, 10, 135-139)

Rodzinnina hipomagnezemii z hiperkaliuciurii i wapnic nerek – opis przypadku i diagnostyka różnicowa

Rodzinnina hipomagnezemii z hiperkaliuciurii i wapnic nerek jest rzadką chorobą dziedziczoną AR o niekorzystnym rokowaniu czynności nerek. Schylokowa niewydolność nerek występuje u 1/3 dorosłych pacjentów, a czas niewydolności nerek wzrasta ze stopniem zaawansowania wapnicy nerek. Molekularną przyczyną choroby jest mutacja genu kodującego proteinę paracellin-1 (claudin-16), której ekspresja stwierdza się w rdzeniowej i korowej części pętli Henle’ego. Proteina ta współtworzy strukturę połączeń międzykomórkowych, ważnych dla okołokomórkowego transportu Mg i 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 hipomagnesemię, hipermagnesiurę, hiperparatyreozę, nieznaczną hipurikemię oraz wapnicy 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 wielomoczczu. Wykluczono nerkową kwasicę cewkową w teście zakwaszania. Ciśnienie tętnicze było w zakresie 95‰. Poza lekkim dodatnim objawem Chwostka, pozostałe badania były w zakresie norm fizjologicznych. Wywiad rodzinny był dodatkowy w kierunku kamicy nerkowej u siostry ojca dziecka. Drugi chłopiec lat 5 został skierowany do szpitala z powodu ostrego bólu brzucha – kolkii nerkowej, badanie rgt jamy brzusznej wykazało znacznie nasiloną wapnicę nerek, badania laboratoryjne były podobne do wymienionych powyżej, nie stwierdzono jednak nadczynności przytarczyc ani nadciśnienia tętniczego. W diagnostyce różnicowej należy wykluczyć wrodzone choroby nerek z utratą magnezu i nasiloną hipomagnesemią: 1. Mutacje receptora Ca-Mg z hiperkaliuciurii, wapnicą nerek i

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• hypomagnesemia
• hypermagnesiuria
• hypercalciuria
• nephrocalcinosis
• renal failure
• differential diagnosis

Słowa kluczowe:
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• hipermagnezemia
• hiperkaliurii
• nefrokalcynoza
• niewydolność nerek
• diagnostyka różnicowa

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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 absorption – 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].

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 consisting 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 ZO1 – 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/ urolithiasis. Significant neurologic symptoms due to hypomagnesemia are not frequent, although the patients can have higher susceptibility to neuromuscular excitability and convulsions. Sometimes also eye symptoms can be present – myopia, nystagmus, choriorietinitis. 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, hypercalcemia 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
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 patients, 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 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 hyperuricemia. 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 hypermagnesia - fractional excretion (FE) of Mg 30.8%, hypercalciuria - calcium/creatinine 1.37, 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 hypererechogenic pyramids of kidney – severe nephrocalcinosis (Figure 2). The liver was slightly enlarged and hypeerechogenic – but liver enzymes were within physiologic range. Basic renal functions - glomerular filtration according to Schwarz was 59 ml/min, tubular resorption tests were within physiologic range. Basic renal functions - glomerular filtration according to Schwarz was 59 ml/min, tubular resorption tests were within physiologic range. Basic renal functions - glomerular filtration according to Schwarz was 59 ml/min, tubular resorption tests were within physiologic range. Basic renal functions - glomerular filtration according to Schwarz was 59 ml/min, tubular resorption tests were within physiologic range.

- **Na (S)**: N
- **Na (U)**: N
- **K (S)**: N
- **K (U)**: N
- **Cl (S)**: N
- **Cl (U)**: N
- **Mg (S)**: N
- **Mg (U)**: N
- **PTH**: N
- **NC**: N
- **PG**: N

**Table I**

<table>
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<tr>
<th>Diagnosis</th>
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<th>Sodium (U)</th>
<th>Potassium (S)</th>
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<th>Chloride (S)</th>
<th>Chloride (U)</th>
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**Figure 3**

Severe bilateral nephrocalcinosis in patient 2 - plain abdominal X-ray.
Salt-losing disorders – Bartter antenatal I, II – or hyperprostaglandin E syndrome – hypomagnesemia is not a typical feature; the main points for differential diagnosis are hypercalciumia 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 are related by hyperprostaglandinemia E – fever, vomiting, intermittent diarrhea. Genetically, the syndrome can be caused by mutations of two genes (clinically indistinguishable): 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-losing 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 hypercalciumia and nephrocalcinosis are not common features. In domethacin therapy is not successful. Ge-netic base is mutation of gene BSND coding protein Bartlin – a beta subunit of the renal magnesium wasting that failed to link to the locus of the mentioned gene. It means that there must exist at least 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-losing disorders – Bartter classi-cal, or type III – hypomagnesemia is present in about 50 % of patients, calcium excre-tion is variable, disturbances are rather pre-senting 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 de-hydration, salts and water depletion, later also growth retardation. Typical laboratory findings are massive NaCl wasting, hypo-chloremic metabolic alkalosis, hypokalemia, and high aldosteron without hypertension. Clinical severity of kidney disease 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 ascend limb of Henle loop and distal convolute tubule. The channel normally mediates flux of Cl ions from the tubular cells to interstitium [6]. Salt-losing disorders – Bartter antenatal I, II – or hyperprostaglandin E syndrome – hypomagnesemia is not a typical feature; the main points for differential diagnosis are hypercalciumia 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, hyper-reninemia. 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renal chloride channels CLCKNB and CLCKNA and present also in K-secretor epithelia of inner ear [2].

Salt losing disorders – Gitelman syndrome – the mildest form of salt losing 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 hypocalcemia, 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 receptor associated disorders – Ca-Mg receptor (CASR) is an important link to calcium and magnesium homeostasis. CASR is located in the apical membrane of parathyroid secreting parathyroidal 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 hypocitraturia, 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, hyper tension 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 isoleucine 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 ultrasound 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 hyperparathyreosysis 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.

Reference