Renal hypomagnesemia, hypercalciuria, nephrocalcinosis

Author: Doctors Iwan Meij1 and Nine Knoers
Creation Date: November 2001
Update: May 2003

Scientific Editor: Professor Udo Wendel

1Department of Human Genetics (417), University Medical Centre Nijmegen, PO. BOX 9101, 6500 HB
Nijmegen, Netherlands. i.meij@antrg.azn.nl

Abstract

Renal hypomagnesemia, hypercalciuria, nephrocalcinosis is a progressive renal disease, characterized by hypomagnesemia, hypercalciuria and nephrocalcinosis. Recurrent urinary tract infections and kidney stones are often observed, and in one third to half of the patients, ocular abnormalities such as horizontal nystagmus, myopia, corneal calcifications and chorioretinitis are observed. Neither chronic oral Mg2+, nor thiazide diuretics can correct serum Mg2+- or urinary Ca2+-levels. Treatment therefore focuses on the prevention of stone formation in these patients. HHN is inherited as an autosomal recessive trait, the gene involved CLDN16 is located in 3q28-3q29. It encodes CLAUDIN16, a 305 amino acid protein with sequence and structural homology to the claudin family of tight junction proteins. Claudins are expressed in a tissue-specific manner, depending on the species. At present, 24 claudins have been identified. They are able to form selective paracellular pathways by both homo- and heteromeric interactions.

Keywords
Renal disease, hypomagnesemia, hypercalciuria, nephrocalcinosis, ocular impairment, CLDN16 gene, CLAUDINS16 protein

Definition/ Clinical criteria

Renal hypomagnesemia, hypercalciuria, nephrocalcinosis (HHN) (OMIM 248250) is a progressive renal disease, characterized by hypomagnesemia, hypercalciuria and nephrocalcinosis. Recurrent urinary tract infections and kidney stones are often observed, and in one third to half of the patients, ocular abnormalities such as horizontal nystagmus, myopia, corneal calcifications and chorioretinitis are observed. Neither chronic oral Mg2+, nor thiazide diuretics can correct serum Mg2+- or urinary Ca2+-levels (Praga et al., 1995; Benigno et al., 2000; Weber et al., 2000). In spite of hypercalciuria, these patients do not show hypocalcemia, which may be due to increased intestinal absorption and bone release of Ca2+. In addition, alternative Ca2+-reabsorption pathways in the kidney may partly correct for the urinary losses of Ca2+. The severity of renal calcification correlates with the development of renal failure (Praga et al., 1995). Treatment therefore focuses on the prevention of stone formation in these patients (Monnens et al., 2000).

Genetics

HHN is inherited as an autosomal recessive trait. Simon and colleagues (1999), identified the gene involved in HHN. They performed a genome wide linkage study in 3 consanguineous kindred's and found a disease locus on chromosome 3q28-29. Characterization of 9 additional families reduced the linkage interval to a 1 cM region between markers D3S1314 and 539-3. Using a positional cloning strategy the

CLDN16 gene (OMIM 603959, formerly known as PCLN-1, cDNA: AF152101, genomic sequence present in AC009520) was cloned. The gene encodes CLAUDIN16, a 305 amino acid protein with sequence and structural homology to the claudin family of tight junction proteins. Claudins are expressed in a tissue-specific manner, depending on the species. At present, 24 claudins have been identified. They are able to form selective paracellular pathways by both homo- and heteromeric interactions (Furuse et al., 1998; Morita et al., 1999; Tsukita et al., 1999). CLAUDIN16 is predicted to be a 4 transmembrane domain protein with intracellular NH2- and COOH-termini, a highly negatively charged first extracellular loop and a PDZ consensus sequence at the C-terminus. Screening of the gene in the 12 kindreds with HHN revealed 10 different mutations. A year later, Weber et al. (2000) identified 6 additional mutations in 8 other HHN families.

Etiology
The CLAUDIN16 protein is specifically expressed in the kidney in the thick ascending limb of Henle's loop (TAL) and the distal convoluted tubule (DCT) (Figures 1A and 1B). It was shown to colocalize with occludin in intercellular junctions of human kidney sections (Simon et al., 1999). Occludin and claudins are components of the tight junction complex and CLAUDIN16 is believed to be an essential component of the selective paracellular pathway for Mg2+- and to a lesser extent Ca2+-reabsorption in the TAL. Its function in the DCT, where the transepithelial voltage difference does not favor Mg2+ reabsorption, is as yet unclear. It is unknown also how the ocular findings in HHN patients can be explained by CLAUDIN16 mutations and why ocular abnormalities are not found in all patients. Studies on the corneal epithelium have demonstrated a paracellular permeability barrier (Huang et al., 1989) and the CLAUDIN16 protein could have a function in the cornea similar to the one in the kidney. A functional role for the claudin16 protein in bovine became apparent when a null mutation (absence of the first four exons) was found in cattle (Hirano et al., 2000; Ohba et al., 2000). In contrast to humans, the animals reported by Hirano et al. suffer from chronic interstitial nephritis (CINFH), characterized by defective filtration and reabsorption. Remarkably, CINFH affected cattle do have hypocalcemia which is not seen in human individuals with CLDN16 mutations.

Figure 1.
A) Magnesium reabsorption in the thick ascending limb is via the paracellular pathway through paracellin B) A model for magnesium reabsorption in the distal convoluted tubule through an apical magnesium channel and a basolateral magnesium transporter. The role of the paracellin protein in this nephron segment is as yet unclear. Active transport is indicated by ~ symbol. Modified from Quamme, 1997.

References


