Rare but Relevant Kidney Disorders

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Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. *Proc Natl Acad Sci U S A* 106: 5842–5847, 2009

Scholl UI, Choi M, Liu T, Ramaekers VT, Häusler MG, Grimmer J, Tobe SW, Farhi A, Nelson-Williams C, Lifton RP

Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *N Engl J Med* 360: 1960–1970, 2009

Bockenhauer D, Feather S, Stanescu HC, Bandulik S, Zdebik AA, Reichold M, Tobin J, Lieberer E, Sterner C, Landoure G, Arora R, Sirimanna T, Thompson D, Cross JH, van't Hoff W, Al Masri O, Tullus K, Yeung S, Anikster Y, Klootwijk E, Hubank M, Dillon MJ, Heitzmann D, Arcos-Burgos M, Knepper MA, Dobbie A, Gahl WA, Warth R, Sheridan E, Kleta R

These two groups of investigators identified simultaneously the same disease, named SeSame and EAST syndrome, respectively, acronyms based on the clinical abnormalities found in this disease (seizures or epilepsy, sensorineural deafness, ataxia, mental retardation and tubulopathy). This new autosomal recessive disorder was described from the study of six kindreds. In four of them, parental consanguinity was documented.

All affected patients initially presented with generalized seizures in infancy. Later, they developed speech and motor delay and marked ataxia. Brain magnetic resonance imaging did not show significant lesions, except volume loss of cerebellum in rare patients. Sensorineural hearing loss was noted from the ages of 1 to 18 yr.

All affected patients had hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. Renin-angiotensin-aldosterone system was stimulated. BP was normal. By ultrasonography, kidneys were normal. Electrolyte imbalance mimics Gitelman syndrome; however, neurologic involvement makes the difference.

Genome-wide linkage analysis was performed on four informative families and identified a single significant locus on chromosome 1q23.2 with a logarithm of odds score of 3.00 and 4.98, respectively. The linked interval contains 70 well-defined and at least six hypothetical genes. Attention was focused on KCNJ10, which encodes the inwardly rectifying K^+ channel Kir4.1, which consists of two transmembrane segments and one pore. KCNJ10 had been shown to be expressed in the central nervous system, cochlea, and distal nephron. A mouse knockout has a neurologic phenotype similar to that seen in the patients.

Various homozygous or compound heterozygous mutations were identified in KCNJ10 in affected patients. Heterologous expression of wild-type KCJN10 in *Xenopus* oocytes resulted in robust currents. In contrast, currents from KCNJ10 mutants were reduced in the study by Bockenhauer *et al*.

In normal mice, the presence of Kcnj10 was demonstrated on the basolateral membrane of the distal convoluted tubule, the connecting tubule, and the early cortical collecting duct. No signal was detected in Kcnj10 knockout mice. These mice die very early as a consequence of central nervous system symptoms. They also had diminished growth, renal salt wasting, and decreased calcium urinary excretion. Conditional knockout in glial cells resulted in death later in life, suggesting that renal salt loss is an aggravating factor in the mice with complete knockout.

Kir4.1/5.1 heteromultimers are located in the basolateral membrane of the distal nephron (more specific, in the distal convoluted tubule, the only tubular site at which inhibition of NaCl reabsorption produces hypomagnesemia and reduced calcium excretion). These multimers recycle potassium that enters the cell *via* the Na^+-K^+-ATPase back into the interstitial space and contribute to the negative membrane potential that promotes basolateral Cl exit. Loss of Kir4.1 activity inhibits the function of Na^+-K^+-ATPase *via* loss of K recycling, reduces basolateral Cl reabsorption by rendering the membrane potential less negative, and thereby inhibits both apical sodium and Cl reabsorption by NCCT and Mg^{2+} reabsorption by TRPM6 because of a less negative membrane potential. The resulting renal salt loss activates the renin-angiotensin-aldosterone system.

In the brain, KCNJ10 seems to be primarily expressed in glial cells. Some Mendelian seizure disorders have already been described, involving K^+ or Na^+ channels.

Kir4.1 is expressed in intermediate cells of the stria vascularis, where it is believed to contribute to the generation of

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the endocochlear potential. As emphasized by Claude Amiel several decades ago, there are many analogies between cochlear and renal physiology and pathology. Single-gene mutations may produce effects on both systems. For example, loss-of-function mutations in ATP6B1, which encodes a subunit of the H^+-ATPase, result in distal tubular acidosis and sensorineural hearing loss. Similarly, mutations in Barttin, which encodes a subunit of some Cl channels, result in both Bartter syndrome and deafness. Not surprising, inherited channel or transporter disorders bridge the gap between medical disciplines and open new avenues for further research (1).

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A missense mutation in the Kv1.1 voltage-gated potassium channel-encoding gene KCNA1 is linked to human autosomal dominant hypomagnesemia. *J Clin Invest* 119: 936–942, 2009

Glaudemans B, van der Wijst J, Scola R, Lorenzoni PJ, Heister A, van der Kemp A, Knoers NV, Hoenderop JG, Bindels RJ

Occurrence of hypomagnesemia (serum Mg^{2+} levels <0.7 mmol/L) in the general population has been estimated to be approximately 2%. The kidney is central for the maintenance of the Mg^+ balance. A large body of knowledge has been generated from the study of inherited defects of renal Mg^{2+} handling. The majority of filtered Mg^+ is reabsorbed along the proximal tubule and thick ascending limb of Henle's loop *via* a passive paracellular pathway. Claudin 16, formerly paracellin 1, and claudin 19 are renal tight junction proteins that are important for paracellular reabsorption of calcium and magnesium in thick ascending limb. Mutations of the corresponding genes, CLDN 16 and 19, result in a rare autosomal recessive tubular disorder that is characterized by familial hypomagnesemia, hypercalciuria, and nephrocalcinosis (FHHNC). This disease is frequently associated with progressive renal failure as a result of both intrarenal calcium deposition and additional roles of claudins in the maintenance of tight junction integrity. Children with a complete loss of function of CLDN16 have a more rapid progression of renal failure than those with residual function (1).

The thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule (DCT) is mutated in Gitelman syndrome. Hypokalemic metabolic alkalosis and hypocalciuria are associated with hypomagnesemia. At the apical membrane of DCT cells is also present the Mg^{2+}-permeable transient receptor potential cation channel, subfamily M (TRPM6). Mg^{2+} uptake from the tubular fluid *via* TRPM6 is primarily driven by the negative potential across the luminal membrane. Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6.

Mutations in FXYD2, encoding the γ-subunit of the basolateral Na^+-K^+-ATPase, is responsible for dominant isolated renal Mg^{2+} wasting, as a result of misrouting of this subunit. This defect has been described so far in a single family (but read this summary to the end). Finally, the recently discovered magnesiotropic hormone EGF causes isolated recessive renal hypomagnesemia (see references in Glaudemans *et al.).*

Glaudemans *et al.* identified a new mechanism for autosomal dominant hypomagnesemia. A large Brazilian family was studied. Twenty-one affected members had serum Mg^{2+} levels <0.4 mmol/L, which was responsible for muscle symptoms and tetany from infancy.

The locus was identified on chromosome 12. The mutation was found in KCNA1, a gene encoding the voltage-gated K^+ channel, Kv1.1. This channel co-localized with TRPM6 along the luminal membrane of DCT. Upon overexpression in a human kidney cell line, patch-clamp analysis revealed that the mutation resulted in a nonfunctional channel, with a dominant negative effect on wild-type Kv1.1 channel function. The negative potential across the apical membrane is normally maintained by an apical K^+ efflux *via* Kv1.1 energized by the action of Na^+-K^+-ATPase. When Kv1.1 function is lost, Mg^{2+} reabsorption in DCT is impaired.

Recently, an unexpected mechanism of renal magnesium wasting and hypomagnesemia was discovered by Adalat *et al.* (2). They first identified a teenager who had hepatocyte nuclear factor 1B (HNF 1B) mutation and presented with tetany and hypomagnesemia (0.620 mmol/L). Then they retrospectively reviewed 91 pediatric cases of renal malformation screened for HNF 1B mutation. Twenty-one had heterozygous mutations. Eight (44%) of 18 mutation carriers had hypomagnesemia (<0.65 mmol/L) compared with one (2%) of 48 of those without mutations. HNF 1B is a transcription factor that is expressed in developing kidneys, whereas, postnatally, proximal and distal tubules express the gene. Hnf 1b in mouse upregulates transcription of various genes whose human homologues are involved in inherited cystic kidney diseases. Adalat *et al.* (2) detected a highly conserved HNF 1B recognition site in FXYD2. They demonstrated HNF 1B–mediated transactivation of FXYD2. Thus, HNF 1B regulates transcription of FXYD2, which participates in the tubular handling of Mg^{2+}. These results extend the phenotype of HNF 1B mutations to include hypomagnesemia. Serum Mg^{2+} levels should be measured in patients with HNF 1B mutations (2).

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Idiopathic retroperitoneal fibrosis: Prospective evaluation of incidence and clinicoradiologic presentation. *Medicine* 88: 193–201, 2009

van Bommel EF, Jansen I, Hendriksz TR, Aarnoudse AL

Retroperitoneal fibrosis: The clinical, laboratory, and radiographic presentation. *Medicine* 88: 202–207, 2009

Scheel PJ Jr, Feeley N

Two regular articles and one commentary are devoted to idiopathic retroperitoneal fibrosis (RPF) in the July issue of *Medicine* (1). This is a good opportunity to brush up our knowledge (and ignorance) on this rare disease. Unfortunately, these two articles discuss only marginally the therapeutic problems raised by this disease.

The prospective study by van Bommel *et al.*, based on 53 cases collected in 10 yr, shows that the annual incidence of 1.3 cases per 100 000 inhabitants in the Netherlands is higher than that previously assumed. Mean age at diagnosis (64 yr; range 34 to 82 yr) was higher than in previous studies and in that by Scheel and Feeley (54.25 yr; range 23 to 74 yr). This is explained by the different inclusion criteria in the two studies (see later).

The clinical presentation of RPF has been known for decades and is confirmed by the findings of the two recent series. Pain (lower back, abdomen, or flank) is the most common symptom, often more severe at night, radiating to the groin or to hip. Weight loss was found in 40% of the patients studied by van Bommel *et al.* In men, testicular pain with or without scrotal swelling is frequent. High erythrocyte sedimentation rate and other markers of inflammation are more pronounced in women than in men. Sixty-six percent of the patients presented with impaired renal function as a result of unilateral or bilateral hydroureteronephrosis.

The diagnosis of idiopathic RPF was based on contrast-enhanced computed tomography (CT) in the study by van Bommel *et al.* and/or magnetic resonance imaging in that by Scheel and Feeley, showing a well-defined soft-tissue density enveloping but not displacing the lower aorta with caudal extension following the bifurcation of the iliac vessels. Malignancy was ruled out on the basis of clinical and radiologic investigations; however, van Bommel *et al.* underlined that localized lymphadenopathies, usually with diameter <1 cm, adjacent to RPF mass were frequently noted. Scheel and Feeley stated that RPF is a form of periarteritis and that all patients who did not meet the aforementioned requirements should undergo biopsy (nine of 53 patients in the series by van Bommel *et al.*).

The main difference between the studies rests on the limits of idiopathic RPF regarding changes of the abdominal aorta: Scheel and Feeley excluded patients with aneurysmal dilation, whereas, in the study by van Bommel *et al.*, 23% of the patients (*versus* 4.6% in a similarly aged healthy population) had aortic aneurysms. This explains why patients of the latter series were older and why men predominate: 41 of 53 were men *versus* 26 of 48 in the former series. This accounts for the striking differences in hypertension and cardiovascular diseases (40% of the patients studied by van Bommel *et al.*) between the studies. This also raises the question of the definition of "idiopathic" RPF: Should patients with increased aortic diameter (60% in the Dutch study) or with atherosclerotic changes be excluded or not from this entity? It is usually considered that RPF is secondary to advanced aortic wall atherosclerosis, possibly through an autoallergic reaction to components of the atherosclerotic plaque. The concept of idiopathic RPF's being a systemic autoimmune disorder has been diversely appreciated and is not supported by the results of van Bommel *et al.* (1).

Four additional morphologic findings emerged from these two recent studies. First, RPF mass can extend up to or above the level of the renal vessels (in three patients, 6% in the Dutch series). Two patients in the series of Scheel and Feeley had significant renal artery stenosis that required endovascular stenting. Iliac artery stenosis or pelvic vein compression or thrombosis may occur in some patients. Five patients (9% in the Dutch study) presented with a bulky mass extending into the pelvis. These atypical forms should be known; biopsy is indicated for these localized tumors. Second, Scheel and Feeley proposed a classification system based on imaging: Class I, RPF surrounding only infrarenal aorta; class II, fibrosis embedding inferior vena cava; class III, lateral extension with compression of one or two ureters; and class IV, extension to the renal hilum. Third, pathologic ^{68}Ga or ^{18}FDG uptake at the level of the RPF plaque was found by van Bommel *et al.* in $>70\%$ of the cases. This demonstrates that the RPF mass is metabolically active and vascularized. Extra-abdominal uptake was noted in 11% of the patients. It would be of interest to know whether the response to steroid therapy correlated with the intensity of the uptake. Fourth, chest CT scanning is valuable in patients with RPF. Uibu *et al.* (2) found that asbestosis was a risk factor for RPF (odds ratio 8.8 for >10 fiber-years). This is confirmed in the prospective study by van Bommel *et al.* Chest CT scans showed unilateral or bilateral pleural plaques or thickening in seven men (17% of the 41 male patients). Six of these seven patients were occupationally exposed to asbestos. No evidence of mesothelioma was found in these patients. Should these cases be considered "idiopathic" RPF? Regarding differential diagnosis, Scheel and Feeley excluded nine patients who did not meet the criteria for diagnosis. Two had aneurysmal dilation of the aorta, one had postsurgical scarring, three had a malignant disease including one lymphoma, and three had Erdheim-Chester disease. This rare non–Langerhans cell histocytosis or juvenile xanthogranulomas may encompass retroperitoneal involvement, in association with bone pain and osteosclerosis, fever, exophthalmos, central diabetes insipidus, and other systemic symptoms (3). Retroperitoneal involvement clearly differs from idiopathic RPF. Atypical soft tissue infiltrates the retroperitoneal space, is less dense than idiopathic RPF, and surrounds the kidneys.

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Thrombomodulin mutations in atypical hemolytic-uremic syndrome. *N Engl J Med* 361: 345–357, 2009

Delvaeye M, Noris M, De Vriese A, Esmon CT, Esmon NL, Ferrell G, Del-Favero J, Plaisance S, Claes B, Lambrechts D, Remuzzi G, Conway EM

The spectrum of predisposing factors to atypical hemolytic uremic syndrome (aHUS) is widening. This syndrome includes cases of HUS that are not linked to Shiga toxin–producing bacteria. Approximately half of the patients with aHUS have mutations in genes that regulate complement system: Either loss-of-function mutations in genes that encode inhibitors of the alternative pathway of the complement system (*e.g.*, factor H or I, CFH or CFI, membrane co-factor protein, factor H–related proteins, C4b-binding protein) or gain-of-function mutations of genes that encode factor B and C3. Antibodies against CFH have been observed in 2 to 10% of patients.

Thrombomodulin is a ubiquitous transmembrane endothelial cell glycoprotein that suppresses clot formation, inhibits fibrinolysis, interferes with inflammation, and inactivates some complement-derived anaphylatoxins.

Delvaeye *et al.* studied 152 patients who had aHUS and were recruited from the International Registry of Recurrent and Familial HUS/Thrombotic Thrombocytopenic Purpura and 380 control subjects. They sequenced the entire coding region of the thrombomodulin gene (THBD), which lacks introns. Six heterozygous mutations of THBD were identified in seven (4.6%) unrelated patients. Two of them belonged to families with aHUS. In one of these families, four heterozygous carriers (including adults) were asymptomatic. As in complement defects, the THBD mutation is not sufficient by itself to cause HUS. Low serum C3 levels were measured in four patients. The disease was evident during childhood, from 6 mo to 15 yr of age. Three of seven patients progressed to ESRD. Four had recurrent aHUS. One patient developed a first episode of aHUS after kidney transplantation at 15 yr of age. Further studies will indicate whether there is a risk for recurrence of aHUS after kidney transplantation.

In vitro studies on cultured cells showed that thrombomodulin provides protection against complement activation. In addition, thrombomodulin binds to C3 and CFH and negatively regulates complement by accelerating CFI-mediated inactivation of C3b in the presence of co-factors CFH and C4b. Cultured cells that express THBD variants that are associated with aHUS had diminished capacity to inactivate C3b and to activate procarboxypeptidase B and thus were less protected from activated complement. In patients with aHUS, genetic testing should include several genes that encode proteins that regulate complement system, including thrombomodulin.