Kidney Diseases: Environmental and Genetic Factors

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The spectrum of hereditary (autosomal dominant) renal cancer syndrome is widening with time. Von Hippel-Lindau (VHL) disease was first to be identified. Attention has been focused on novel localizations of VHL disease (in addition to central nervous system and retinal involvement, bilateral and multifocal renal cell carcinoma [RCC], and pheochromocytoma), such as pancreas cysts and tumors and, more recently, endolympathic sac tumors, causing irreversible sensorineural hearing loss as a result of intralabyrinthine hemorrhage (1).

Then, the Birt-Hogg-Dube (BHD) syndrome, first described in 1977, was better recognized, and its molecular basis was identified in recent years. This syndrome comprises skin fibrofolliculomas, kidney neoplasms (chromophobe carcinoma, oncocytoma, or mixed tumors), lung cysts, and spontaneous pneumothorax. The BHD gene is located at chromosome 17p, and its product has been called folliculin. Two recent studies stressed the frequency of lung involvement (2,3). Among 198 patients from 89 families with BHD syndrome, 25% had a history of pneumothorax (2). The BHD syndrome can occur as an isolated phenotype with pulmonary involvement (3). The risk for subsequent development of renal neoplasms should be remembered.

In the more recently described (in 2001) hereditary cancer syndrome, affected individuals are at risk for cutaneous and uterine leiomyomas and kidney cancer (hereditary leiomyomatosis and RCC [HLRCC]). These individuals are characterized by heterozygous mutations of the fumarate hydratase gene, located at 1q. Fifty-six families have been studied in North America by Grubb et al. in National Institutes of Health laboratories. Skin lesions appear as firm, flesh-colored to light red/brown papules or nodules, with onset typically in the third decade of life. Grubb et al. underline the aggressive nature of the renal tumors. These tumors may be isoechoic by ultrasonography and may therefore be missed. Overall, nine (47%) of 19 patients presented with nodal or distant metastases. At a median follow-up of 34 mo, 10 (53%) of these 19 patients had died of kidney cancer or had advanced disease. Parenchymal-sparing surgery, often advocated in other hereditary renal cancer syndromes, may not be appropriate for patients with HLRCC syndrome.

Among 40 renal tumors resected from 38 patients (from 17 to 75 yr of age) belonging to families with HLRCC, papillary carcinomas predominated (25 cases), followed by tubulopapillary, tubular, and mixed patterns. The histologic hallmark of these tumors is the presence of a characteristic large nucleus with very prominent inclusion such as orangophilic or eosinophilic nucleolus, surrounded by a clear halo. Proper diagnosis of these tumors by the pathologist may assist in early detection of HLRCC syndrome (4).

Adequate diagnosis of these hereditary renal cancer syndromes is of great importance for at-risk individuals in these affected families. Genetic testing allows identification of carriers of the mutation and establishment of appropriate follow-up and early diagnosis of renal cancer.

References


Despite extensive research, the cause of endemic (Balkan) nephropathy (EN) has remained obscure for decades. This chronic tubulointerstitial disease is found in Bosnia, Bulgaria, Croatia,
Romania, and Serbia and occurs exclusively in farming villages located in valleys of Danube River tributaries. The renal disease has a strong association with urothelial cancer, involving mainly the upper urinary tract. The role of various environmental toxins, including, most recently, ochratoxin A, has been widely explored.

The clinical presentation of EN is strongly reminiscent of aristolochic acid (AA) nephropathy (previously termed Chinese herb nephropathy). Indeed, the early cases of renal failure rapidly progressing to ESRD were reported in Brussels, Belgium, in 1992 occurring in women taking daily slimming pills containing root extracts from Chinese herbs. In these herbs, Stephania tetrandra had been inadvertently replaced by Aristolochia fangchi. Renal tissue samples from patients exposed to these herbs contained specific AA-DNA adducts. aristolactams (AL), activated metabolites formed by AA nitroreduction, are also able to form DNA adducts. Urothelial carcinoma represents a late and frequent complication of AA nephropathy. Prophylactic removal of native kidneys and ureters has been advocated for these patients (1).

The data collected by Grollman et al. strongly suggest that AA toxicity is responsible for EN. In the endemic region of Croatia, Aristolochia clematitis often grows in cultivated fields, where its seeds commingle with wheat grain during the annual harvest. Thus, residents of this region who ingested home-baked bread prepared from contaminated grain may be exposed, over a period of years, to toxic amounts of AA.

Grollman et al. first identified and quantified AL-DNA adducts from the kidneys of an American woman who developed ESRD after use of an herbal remedy containing AA (showing that AA nephropathy is not limited to Brussels). AL-DNA adducts have also been detected in renal tissues of four patients with EN, as well as in upper urinary tract transitional cell cancer of three long-term residents of endemic villages. Transitional cell carcinomas from 11 patients, who had resided in endemic villages for a minimum of 15 yr, also had p53 mutational analysis. AL-DNA adducts give rise to a specific pattern of mutations in the p53 gene. The frequency of A:T → T:A mutations of p53 in transitional cell carcinomas in patients with EN or suspected EN is high (78%), whereas it is much lower (approximately 5%) in non–EN-related urothelial carcinomas. Experimental data have confirmed the nephrotoxic and carcinogenic effects of Aristolochia (1).

The same toxin, AA, may be responsible for chronic tubulo-interstitial kidney disease and urothelial carcinoma, resulting from either herbal therapy or intake of contaminated bread. These findings remind us that (1) traditional herbal therapy may be toxic and should be submitted to quality controls, similar to any other pharmaceutical product; and (2) environmental toxins may be the cause of endemic disease. Beware: Familial cases may be due either to inheritance or to shared environmental factors!

References


Edghill EL, Oram RA, Owens M, Stals KL, Harries LW, Hattersley AT, Ellard S, Bingham C

A new autosomal dominant kidney disease, characterized by mutations of the TCF2 gene, encoding hepatocyte nuclear factor-1β (HNF-1β), emerged in approximately 2000. It became a common cause of chronic kidney disease as stated by Edghill et al. among 160 patients (ranging from 1 to 78 yr of age) with unexplained renal disease; 38 (24%) had TCF2 mutations.

The renal disease is quite variable with a wide spectrum of clinical presentations: Fetal hyperechogenic kidneys, like other cystic kidney diseases of early development; multicystic dysplasia; isolated cystic kidney disease, including glomerulocystic disease; cystic hypo/dysplasia; single kidney; and horseshoe kidney (1). The diagnosis is often made in children but is often missed in adults, in whom the presentation may be less typical (2). Only a few renal cysts may be found, as in many chronic kidney diseases. In contrast, kidney involvement may mimic autosomal dominant polycystic kidney disease (3). The rate of renal progression is very heterogeneous even within a given family. Renal failure may develop in early childhood. In other cases, renal disease is very slowly progressive, beyond 50 to 60 yr of age.

Extrarenal manifestations may facilitate the diagnosis. TCF2 mutations were first described in 1997 as causing maturity-onset diabetes of the young type 5 (MODY5); however, renal disease often precedes diabetes. Renal involvement is different from diabetic nephropathy. Pancreatic atrophy is commonly found, and exocrine dysfunction may occur. Genital tract abnormalities (uterine malformations, agenesis of vas deferens) are more rarely found. Early hyperuricemia and gout mimic familial juvenile hyperuricemic nephropathy (as a result of uromodulin or Tamm Horsfall protein mutations). Finally, liver test abnormalities are detected in some patients.

All of these manifestations can be classified as disorders of the development of kidney, pancreas, liver, and genital tract. Indeed HNF-1β is a transcription factor, regulating gene expression in these various organs, and is involved in early embryogenesis.

The wide spectrum of clinical manifestations of the TCF2/HNF-1β-linked disease makes the diagnosis difficult, more specifically in adults. Some patients’ disease is first diagnosed by diabetologists, others by nephropediatricians or by adult nephrologists. Genetic testing is thus crucial for adequate diagnosis and counseling.

Regarding genetics, clinicians should be aware that 32 to 58% of mutations arise spontaneously, de novo, in the absence of positive family history. In approximately 50% of the cases, coding region/splicing mutations of TCF2 are found. Edghill et al., as well as other authors, found a high frequency of whole TCF2 gene deletions by using a very sensitive technique for gene dosage analysis: Multiplex ligation-dependent probe am-
plification assay (2). Geneticists should be aware of this finding. Specific methods (both sequencing and gene dosage analysis) should be used so as not to miss complete deletions. Because de novo mutations are frequent, a family history of kidney disease or diabetes should not be considered as a prerequisite for molecular genetic testing. Finally, although TCF2/HNF-1β was initially described as a MODY gene, patients usually present with renal disease rather than with MODY.

References


Atypical hemolytic uremic syndrome (aHUS; *i.e.*, not caused by infection with Shiga toxin–producing *Escherichia coli*, *Streptococcus pneumoniae*, HIV, malignancy, and drugs) accounts for 10% of all cases of HUS and is often associated with defective complement regulation. Approximately 60% of patients with aHUS have mutations in the genes of proteins that regulate complement alternative pathway and protect host cells from complement activation: Membrane co-factor protein (MCP or CD46), a membrane-bound protein anchored in most cell membranes (except erythrocytes), and four fluid-phase proteins, factor H (CFH), factor I (CFI), factor B, and C3 (1). Recently, deficiency of CFH-related proteins (CFHR1 and CFHR3) was found to be associated with CFH autoantibodies in 11% of 147 patients with aHUS (2).

MCP mutations were found in 15% of patients with aHUS in the study by Sellier-Leclerc et al. The study by Fang et al. broadens the clinical spectrum of diseases associated with MCP mutations. They studied more specifically the phenotypes of 10 patients carrying two mutations, either R69W or A304V, in the homozygous or heterozygous state, isolated or not. Indeed, in three patients, MCP mutations were associated with CFI mutations. Of interest, MCP serves normally as a co-factor for CFI to inactivate C3b and C4b on the cell membrane.

Six patients presented with aHUS, four of whom had recurrent episodes. Two patients had no renal sequelae, whereas one had persistent proteinuria and one progressed to ESRD by age 7. The clinical presentation in the remaining four patients was heterogeneous. A 63-yr-old man had clinical manifestations suggestive of either aHUS or thrombotic thrombocytopenic purpura. A 4-yr-old girl developed fatal Shiga toxin–HUS (with borderline low serum C3 level). A 30-yr-old woman had HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome during a second pregnancy and developed chronic renal failure 1 yr later. Finally, a 22-yr-old man presented with glomerular disease characterized by isolated C3 deposits. Thus, mutations of proteins that regulate complement alternative pathway may represent factors predisposing not only to aHUS but also to syndromes such as HELLP and thrombotic thrombocytopenic purpura, which share clinical similarities and endothelial cell dysfunction, leading to thrombotic microangiopathy.

Fang et al. developed permanent Chinese hamster ovary cell lines expressing either control or mutated MCP. These cells were complement “challenged,” and C3 fragment deposition was monitored. They demonstrated that both R69W and A304V MCP mutations were deficient in their ability to control the alternative pathway of complement activation on a cell surface.

Atypical HUS caused by MCP mutations has some peculiarities, underlined by Sellier-Leclerc et al.: No patients had onset before age 1; these patients have a relapsing course, and relapses often have a spontaneous favorable outcome. Sixty to 86% of patients have functioning kidney 4 to 5 yr after onset. The remaining patients progressed to ESRD and required kidney transplantation. Because MCP is a membrane-bound molecule, it is expected that the risk for post-transplantation recurrence is low. Recurrence has been reported, however, in two of 10 patients who received a transplant. Endothelial microchimerism may be involved in these cases.

In contrast, aHUS as a result of factor H (CFH) mutations is often clinically severe and leads to end-stage renal failure in >80% of cases, and kidney transplantation is often complicated (80%) by thrombosis or HUS recurrence. Plasma CFH is produced nearly totally by the liver. In most patients with aHUS and heterozygous CHF mutations, the mutated protein is believed to interfere with the function of the normal counterpart, leading to uncontrolled complement ac-
tivation. Hepatectomy and liver transplantation would therefore eliminate the synthesis of the mutated protein and at the same time provide normal CFH. The outcome of the first combined liver-kidney transplantations has been poor. Recently, encouraging results were obtained by using intensive plasma exchange therapy before, during, and after transplantation. This program was achieved by Jalanko et al. (3) in a 12-mo-old boy and his 16-yr-old aunt with aHUS occurring 6 mo apart and heterozygous CFH mutation. In both cases, combined liver-kidney transplantation was successfully performed. All four grafts started to function immediately. No recurrence occurred after 15 and 9 mo of follow-up, respectively. Anticoagulation was started a few hours after the operation. The Leiden mutation in the first patient was regarded as an additional indication for long-term anticoagulation. On the basis of these two cases and of one previously reported, this protocol seems to be a promising treatment option for patients who have aHUS and CFH mutations, whose prognosis otherwise is very poor.

References