
Epidemiologic studies of rare diseases may produce surprising findings and raise ethical issues. This is illustrated in this study performed in 171,977 consecutive Taiwanese newborns (including 90,288 boys) from July 2006 through June 2008 by measuring dry blood spot and then leukocyte α-galactosidase A (α-Gal A) activities and finally by detecting mutations in the GLA gene involved in Fabry disease. Schematically, two phenotypes of this disease are known: the classic form, with systemic involvement and very low α-Gal activity in males; and the later-onset form (>40 years of age), with some residual α-Gal A activity, which is dominated by cardiac involvement.

All 11 newborns who had <5% of normal mean α-Gal A activity were boys who had GLA mutations. In the group of 66 newborns (64 boys and 2 girls) with α-Gal A activities between 5% and 30%, 61 hemizygous boys and 2 heterozygous girls had GLA mutations. Among the group of 12 newborns (11 boys and 1 girl) with α-Gal A >30%, only 1 boy had a previously reported mutation, identified in a family with later-onset renal disease.

In total, 72 male and 2 female newborns had GLA mutations, an overall frequency of approximately 1 in 1250 boys and approximately 1 in 40,840 girls. Four boys were “predicted” to have the classic phenotype, a frequency of about 1 in 22,570 newborn boys. In contrast, the estimated frequency of the later-onset phenotype is approximately 1 in 1390 male newborns. Three families provided information on other members of the kindreds, two with classic and one with later-onset phenotype. All three families had previously undiagnosed symptomatic family members, including one heterozygous female with ESRD and two males with renal involvement. This is undoubtedly the positive side of such studies.

A second study was performed more recently in 110,027 Taiwanese newborns between January 2008 and January 2009 by using a similar protocol (plasma α-Gal A activity was measured) (1). The results of this study confirmed those of the previous screening. A high prevalence of the cardiac variant Fabry mutation IVS4 + 919G→A, first discovered in Japanese patients, was found among newborns (approximately 1 in 1600 boys) in both studies. This splicing mutation was most common (82% of patients). The alternatively spliced transcript was normally present in small amount (<5% of normal transcript) in most human tissues. However, the G→A transversion enhanced the percent expression of the alternatively spliced α-Gal A variant and included a 57-nucleotide intronic sequence that caused a frameshift mutation, resulting in a truncated enzyme polypeptide that had no detectable enzyme activity.

The clinical significance of this splicing mutation remains to be fully clarified. Of interest, Lin et al. (1) have investigated 9 grandfathers and 11 grandmothers carrying this mutation, as do their respective grandsons. Among the 9 maternal grandfathers, only 3 had hypertrophic cardiomyopathy, compared with none of the 11 grandmothers.

These results should be compared with those reported in 2006 from Torino, Piedmont, Italy, by Spada et al. (2). They screened 37,000 consecutive newborns with similar methods and identified 12 infants with GLA mutations, including 11 who had molecular lesions that expressed residual activity consistent with the later-onset phenotype. The overall frequency of Fabry mutations was approximately 1 in 3100 Caucasian boys. Mutation analysis predicted that one of the newborns had the classic phenotype (1 in approximately 37,000), whereas 11 of the newborns were predicted to have the later-onset phenotype (1 in approximately 3400). The prevalence of the classic form is close to that found in previous estimations, whereas that of the later-onset phenotype seems to be higher than commonly thought. In Taiwan, the frequency was 2.5 times more frequent than in the Italian population.

These studies raise many ethical and clinical issues. What can be said to the parents of neonates harboring a GLA mutation suggestive of a later-onset disease? The clinical consequences of some mutations, if any, cannot be predicted. The ethnic background should be taken into account. If clinical consequences can be expected, when to start evaluating the cardiac condition and when to consider enzyme replacement therapy, if necessary? What are the psychologic consequences of the screening on the mutation carrier and his/her family? The ethical issues raised by early detection and prediction of later-onset genetic

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disease should be debated, not only by experts, but also with the general population.

References


Van Keimpema L, Nevens F, Vanslembruch R, Van Oijen GH, Hoffmann AL, Dekker HM, De Man RA, Drenth JPH

Massive polycystic liver may be the source of severe discomfort, early satiety, pain, dyspnea, and finally denutrition. This is in part due to the increase with age in the number of hepatic cysts, but also because the individual cyst volume grows from 0.25 to 22.8 ml over 20 years. Polycystic liver is found in two inherited disorders—autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (PCLD), an infrequent disorder in which no kidney cysts are detected caused by mutations in PKRCSH or SEC63 genes. Studies in ADPKD have indicated that total liver cyst volume and the prevalence of massive polycystic liver are greater in women than in men.

Liver cysts arise from cholangiocytes. Secretin is a potent stimulator of adenylate cyclase and thus of cAMP generation. cAMP acts by two major mechanisms: increased electrolyte and water secretion and stimulation of cholangiocyte proliferation. Conversely, somatostatin inhibits cAMP production and thus fluid secretion and proliferation.

Additional experimental and clinical data supported the project of initiating a clinical trial of somatostatin analogues on liver cyst progression. Octreotide, a somatostatin analogue, prevented outgrowth of liver and kidney cysts in polycystic kidney (PCK) rats. In contrast, antagonists of the V2 vasopressin receptor have no effect on liver cysts that do not express this receptor, whereas they prevent or slow the progression of renal cysts in various experimental models. In two patients with polycystic livers, a 3- to 6-month treatment with somatostatin analogues led to impressive reductions in liver volume (1). Finally, a randomized, placebo-controlled trial in ADPKD patients using slow-release octreotide (40 mg) showed that kidney volume increase could be reduced by 60% at 6 months compared with placebo but there was an ongoing increase of kidney volume—2.2% in the octreotide group versus 5.9% in the placebo group (2).

Van Keimpema et al. (1) designed a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effects of the long-acting somatostatin analogue, lanreotide autosolution (120 mg), or placebo administered subcutaneously every 28 days for 24 weeks in patients with polycystic liver due to ADPKD (32 patients) or PCLD (22 patients). The high percentage of PCLD is explained by the fact that the initiators of and participants in this trial were gastroenterologists and hepatologists. The primary end point was change in liver volume measured on computed tomography (CT) scan at baseline and after 24 weeks of treatment. Health-related quality of life was a secondary end point. Of 113 consecutive patients assessed during the study period, 54 were included in the trial. Relatively more PCLD patients (68%) than ADPKD patients (38%) received lanreotide.

The mean liver volume decreased from 4606 to 4471 ml (i.e., an average reduction of 2.9%) whereas there was an average increase of 1.6% in patients receiving lanreotide and in those in the placebo group, respectively. Eighty-five percent of patients on lanreotide showed a decrease of liver volume, compared with 27% of those receiving placebo. Larger livers had proportionally more volume reduction than smaller livers. In the subgroup of patients with ADPKD, mean kidney volume decreased by 1.5% with lanreotide, whereas it increased in the placebo group ($P = 0.02$). Current health perception improved in lanreotide-treated patients. The most common adverse effect of lanreotide consisted of loose, pale, and fatty stools (19 patients), which were relieved by pancreatic enzymes. Gamma-glutamyl transferase levels increased in the lanreotide group, possibly reflecting increased cyst epithelium degeneration. In this trial, no correlation was found between lanreotide serum levels and response to treatment. Little is known about the optimal dosage of somatostatin analogues. The authors chose for the highest licensed dose of lanreotide. Lanreotide at 120 mg is equivalent to octreotide at 60 mg. However, somatostatin receptor affinity of octreotide is higher compared with that of lanreotide.

The results of this trial are very encouraging. Aspiration and sclerosis, laparoscopic fenestration, or hepatic resection have led to disappointing or limited results in women with massive polycystic liver. Combined liver and kidney transplantation has been mandatory in some of them. Noninvasive effective therapy is eagerly awaited. Another trial with a somatostatin analogue is in progress.

References


Aalamovitch S, Plaisier E, Favrole P, Prost C, Chen Z, Van Agraemel T, Marro B, Ronco P

The clinical heterogeneity of genetic diseases characterized by well identified mutations is a striking feature. The diseases
related to COL4A1 mutations are a new example of this statement.

The COL4A1 gene codes for the α1 chain of type IV collagen (α1(IV)), a major ubiquitous component of basement membranes. Mutations in this gene were first reported by neurologists in families with autosomal dominant forms of porencephaly. The porencephalic cavity is caused by cerebral hemorrhage that occurred during the intrauterine or neonatal period. A broad range of neurologic features have been reported, including infantile hemiplegia, mental retardation, and hemorrhagic strokes in children or in adults that are triggered by trauma or anticoagulation.

In another group of patients, cerebral small vessel disease (CSVD) predominates, with leukoencephalopathy, lacunar infarcts, and micro- or macrobleeds without porencephaly. Various eye abnormalities may be found, including retinal arteriolar tortuosity, cataract, or anterior segment dysgenesis of the eye (Axenfeld–Rieger anomaly). This CSVD is reminiscent of the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) because of mutations in the NOTCH 3 receptor. Rare cases of CADASIL syndrome associated with renal involvement have been reported. Electron microscopic analysis showed pathognomonic granular osmiophilic material in cerebral, cutaneous, and intrarenal arteries. Immunohistochemistry using an antibody specific for the NOTCH 3 ectodomain showed positive granular staining in the same vessels, whereas no staining was found in a patient with common nephroangiosclerosis (1). In addition, hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS) was reported in 1997 and is caused by mutations in the TREX1 transcription factor (2). This represents a distinct subtype of retinal vasculopathy with cerebral leukodystrophy.

The third mode of presentation of COL4A1 mutations has been described by Plaisier et al., and the patients first presented with renal disease (3). This autosomal dominant entity has been named HANAC syndrome, or hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (3). Mutations affect glycine residues in close proximity in exons 24 and 25 within the triple-helix domain of the protein. The main phenotypic features encompass a nephropathy with hematuria or bilateral renal cysts, a muscular disease with cramps, and retinal arterial tortuosity. Skin and kidney biopsies show by electron microscopy abnormal thickening, multilamination, and/or focal disruption of the basement membranes.

In their recent study, Alamovitch et al. collected data on the neurologic condition of 14 HANAC patients (ranging from 22 to 57 years of age) belonging to three unrelated families. Nine were interviewed and examined. For the four deceased subjects (ages at death ranging from 60 to 69 years), the causes of death were not neurologic. One patient declined to participate in this study. No patient had infantile hemiparesis, mental retardation, history of stroke, or spontaneous subarachnoid or intracerebral hemorrhage. Only two patients had a history of cerebrovascular injury: acute cerebellar ataxia in one and posttraumatic cerebromeningeal hemorrhage in the other.

In nine patients, brain magnetic resonance imaging (MRI) was performed and all showed at least one abnormality. No porencephaly was observed. Multiple intracranial aneurysms (ICAs) were found in three patients; these ICAs were small, asymptomatic, and localized on the intracranial carotid at the level of the carotid siphon. Seven patients had MRI abnormalities consistent with CSVD dominated by leukoencephalopathy. No cortical involvement was detected. HANAC syndrome therefore constitutes a new monogenic cause of familial ICAs. Of interest, two other inherited diseases with syndromic ICAs have been identified: autosomal dominant polycystic kidney disease and Ehlers–Danlos syndrome type IV with mutations in COL3A1. Regarding diagnosis, skin vessels changes have been described in three autosomal dominant angiopathies: CADASIL, HERNS, and HANAC. Skin biopsy analysis may provide a cost-effective guide before practicing an expensive and time-consuming gene screening.

These entities such as HANAC or CADASIL syndromes can be considered as “systemic basalopathies.” They also opened the field of renal angiopathies/nephrosclerosis/nephrango-sclerosis by using new tools of investigation and by suggesting more pathophysiological heterogeneity than previously thought.

References


Surprisingly, inherited disorders due to mutations of the genes coding for the renin-angiotensin system (RAS) have been rarely reported. The most striking example is autosomal recessive tubular dysgenesis, characterized by the absence or paucity of proximal tubules and caused by various mutations involving renin, angiotensinogen, angiotensin converting enzyme (ACE), and angiotensin AT1 receptor (1). In most cases this disease
results in early end-stage renal failure. This disease is reminiscent of the cases of renal tubular dysgenesis occurring in fetuses exposed to ACE inhibitors or angiotensin receptor blockers, or in ischemic fetal kidneys in the twin-to-twin transfusion syndrome (1).

Zivna et al. have studied three families with dominant renin gene mutations: a deletion in two unrelated families, and a missense mutation in the exon 1 coding for the signal sequence in the third family. The gene responsible for renin production is located on chromosome 1 and is primarily expressed by granular cells in the juxtaglomerular apparatus. The gene product, preprorenin, contains a signal sequence that directs endoplasmic reticulum (ER) targeting, glycosylation, and proteolytic processing of the nascent preprorenin, resulting in prorenin and renin. Transfection and in vitro studies have demonstrated that both mutations affect ER translocation and processing of nascent preprorenin, accounting for reduced or abolished biosynthesis and secretion. Kidney biopsies were available in three patients with the deletion. Light microscopy examination revealed focal tubular atrophy and dystrophy, focal segmental glomerulosclerosis, and interstitial fibrosis. Immunohistochemical study showed decreased staining for renin and prorenin in juxtaglomerular granular cells and tubular epithelia. However, abnormal localization of renin and prorenin inside of the vessel wall of several arterioles and small arteries was detected. Staining intensities of the other RAS components were decreased.

The description of the phenotype of this disease was based on the study of 16 affected subjects. The ages at diagnosis ranged from 4 to 59 years. The phenotype included anemia (responsive to erythropoietin), hyperuricemia (usually mild, not accompanied by gout, present in many but not all patients), and slowly progressive chronic kidney disease. Plasma renin and aldosterone levels were low but not entirely suppressed. Increased proximal tubular reabsorption due to mild volume depletion may be responsible for reduced fractional excretion of uric acid and hyperuricemia. By ultrasonography, kidneys were atrophic with no evidence of cysts. End-stage kidney disease developed between 43 and 68 years of age.

Although hyperuricemia is mild and inconstant, this disease should be added to the group of inherited kidney diseases with early hyperuricemia: familial juvenile hyperuricemic nephropathy due to UMOD mutations, which codes for uromodulin, and hepatocyte nuclear factor 1, homeobox b (HNF 1-β) mutations disease, which is characterized by renal cysts, diabetes mellitus, genital or renal malformations, early gout, and liver test abnormalities (but the phenotype is rarely complete). These two diseases have an autosomal dominant inheritance.

References


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Genetic studies of hereditary forms of nephrotic syndrome have led to the identification of proteins playing a crucial role in slit-diaphragm signaling [e.g., nephrin, podocin, phospholipase Cε1, CD2 adaptor protein (CD2AP), and transient receptor potential cation channel 6 (TRPC6)], regulation of actin cytoskeleton dynamics (such as α-actinin-4, and nonmuscle myosin heavy chain type II isoform A), maintenance of podocyte integrity (nuclear or mitochondrial proteins), and cell-matrix interactions (such as laminin β2). Mutations in the genes coding for these proteins lead to inherited kidney diseases, the prototypes of which are of congenital or infantile-onset and autosomal recessive (mutations in NPHS1 and NPHS2 that encode nephrin and podocin, respectively) (1). Recent studies have shown that adult-onset nephrotic syndrome may occur not only in autosomal dominant forms (ACTN4 coding for α-actinin-4), but also in some atypical forms of autosomal recessive diseases (1). Santin et al. have reported nephrin mutations causing adult-onset focal segmental glomerulosclerosis (FSGS); one patient was 27 years old at onset of the disease (2).

Brown et al. have added further complexity to the spectrum of autosomal dominant FSGS, the lesion frequently found in patients with inherited nephrotic syndrome. From the study of two families, they have identified a locus for FSGS on chromosome 14q32. Fifteen genes have been sequenced in the region of interest. A sequence variant within the same exon of the formin gene INF2 that segregated with disease was found. The mutation occurred de novo in family 1.

Sequence of INF2 was subsequently performed in 91 unrelated individuals with familial FSGS. In probands from nine additional families, point mutations were identified in INF2. In five families, some younger individuals carrying these point mutations had no increase in urine protein, consistent with reduced, age-related penetrance, similar to the phenotypes associated with TRPC6 and ACTN4 mutations.

Of interest, the phenotypes in families with INF2 mutations share certain features. Individuals with mutations present in early adolescence or adulthood, typically with moderate proteinuria. Nephrotic-range proteinuria may develop but no affected individual had full-blown nephrotic syndrome. Microhematuria and hypertension were found in some patients. Proteinuria and disease were progressive, often leading to ESRD.

On renal biopsies, changes were categorized as “FSGS, not otherwise specified.” No glomerular hypertrophy was noted. By electron microscopy, prominent actin bundles were uncommonly found within the foot processes.

In situ hybridization and antibody staining in adult normal kidney showed INF2 expression in the podocytes (as well as in a pericapillary pattern), predominantly in the perinuclear region. INF2 localizes in the ER in fibroblasts. Cultured podocytes transfected with wild-type (WT) or mutant INF2 constructs were examined. Podocytes transfected with the WT construct showed
perinuclear INF2 staining, whereas podocytes transfected with mutant INF2 showed a different localization pattern, with a finer, more diffuse distribution. WT and mutant forms co-stained with phalloidin, consistent with the notion that these proteins induced actin polymerization. Formins are a family of proteins that accelerate actin filament assembly.

Podocytes are complex, actin-rich, interdigitating structures. Dysregulation of the podocyte cytoskeleton is a common feature of glomerular disease state. It may be hypothesized that individuals harboring disease-associated INF2 mutations have a defect in actin-mediated podocyte structural maintenance and repair.

References
