Anderson-Fabry Disease: Its Place among Other Genetic Causes of Renal Disease

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In the last two decades, decisive advances have been made in the field of human genetics, including renal genetics. The responsible genes have been mapped and then identified in most monogenic renal disorders by using positional cloning and/or candidate gene approaches. These approaches have been extremely efficient since the number of identified genetic diseases has increased exponentially over the last 5 years. The data derived from the Human Genome Project will enable a more rapid identification of the genes involved in the remaining “orphan” inherited renal diseases, provided their phenotypes are well characterized. We have entered the post-gene era. What is/are the function(s) of these genes? What are the molecular partners of the gene product? What is the disease mechanism, and how is the normal cascade of events disturbed when the gene is altered by a mutation? The main challenge in many renal genetic diseases, including autosomal dominant polycystic kidney disease (ADPKD), is to design pharmacologic means to complement/substitute or to bypass defective steps and thus modify the clinical course of the disease. These steps have been accelerated in a few genetic disorders, such as Anderson-Fabry Disease (AFD), including research on gene therapy.

Two Lysosomal Diseases Involving the Kidney: AFD and Cystinosis

It is interesting to compare the different genetic approaches used in two lysosomal diseases with kidney involvement, AFD and cystinosis. In cystinosis, clinical manifestations occur in early childhood, whereas they appear after 5 years of age or later in AFD. Both diseases are characterized by intralysosomal accumulation of a substance, due to either deficient degradation (AFD) or defective egress (cystinosis). AFD, first described in 1898, is an example in which a classical genetic approach has been possible, starting from the enzyme and moving to its gene and, recently, to the production of human α-galactosidase A for enzyme replacement therapy (see Branton et al. in this issue).

Nephropathic cystinosis, first described in 1903, is an autosomal recessive disorder characterized by the intra-lysosomal accumulation of cystine. It is caused by a defect in the transport of cystine out of the lysosome, a process mediated by a carrier that remained unidentified for several decades. However, an important management step was devised in 1976, before the biochemical defect was characterized in 1982. Indeed cysteamine, an aminothiol, reacts with cystine to form cysteine-cysteamine mixed disulfide that can readily exit the cystinotic lysosome. This drug, if used early and in high doses, retards the progression of cystinosis in affected subjects by reducing intralysosomal cystine concentrations. The gene involved in cystinosis was mapped later in 1995 on chromosome 17p. Three years after that, the gene was identified by using positional cloning, and called CTNS. Mutations in CTNS were detected in affected subjects. CTNS codes for a seven-transmembrane domain protein called cystinosin, which is an integral lysosomal membrane protein (1). Ctns, the murine homologue of CTNS, has been cloned, opening the possibility to generate knock-out mice, mimicking human cystinosis, and to design new and curative therapeutic approaches (2).

Epidemiology of AFD among Other Monogenic Kidney Diseases

Data on monogenic disease frequency are often difficult to analyze, not only because of geographic/ethnic differences between populations, but also because of methodologic differences, the classical parameters used in epidemiology (i.e., disease incidence, disease prevalence, and birth prevalence) being frequently confused (3). These difficulties are maximal when diseases are rare. In X-linked diseases, such as AFD, the variability of clinical features in carrier females presents another obstacle to determining estimations. In addition, whereas some information on frequency of classical AFD is available, such information is lacking for both the “cardiac” and the “renal” variants of AFD, in which cardiac and renal features respectively predominate. The latter forms have been reported throughout the world, like the classical form, but there has been a more systematic search for them in Japan. The cardiac variant was diagnosed in 7 (3%) of 230 unrelated Japanese males, with previously unexplained left ventricular hypertrophy (4,5).

AFD among Lysosomal Storage Diseases

The frequency of AFD among lysosomal storage diseases can be estimated from the reports of reference laboratories for the diagnosis of such diseases throughout the world. It ranges
from 2.8 to 7.7% (5–7). The number of cases of AFD related to demographic data (i.e., the number of live births during the study period) enabled the authors to estimate birth prevalence. It should be noted, however, that identifying cases through a screening laboratory leads to an underestimation, because ascertainment is probably far from complete. An approximate AFD birth prevalence was estimated to 0.09 per 10,000 live births in Australia (5), 0.02 in the Netherlands (6), and 0.03 in British Columbia, Canada (7). These three populations are mainly Caucasian.

Table 1 summarizes data on birth prevalence evaluated through newborn-population surveys in cystinosis, nephronophthisis, and Alport syndrome. In ADPKD, there is obviously no study on birth prevalence. However, risk on the one hand and heterozygote frequency on the other hand may be considered equivalents of ADPKD birth prevalence (3). Epidemiologic data on renal replacement therapy among patients with AFD are presented in the article by Obrador et al. in this issue.

**AFD among Lipidoses**

AFD also belongs to the group of renal lipidoses, of which it is the most prevalent disease (8). Renal involvement is very rare in Gaucher disease, another lysosomal disease, in which it occurs mostly after splenectomy. This group includes lecithin-cholesterol acyltransferase (LCAT) deficiency, lipoprotein glomerulopathy, and various extremely rare inherited diseases. Familial LCAT deficiency is an autosomal recessive disorder characterized by corneal opacities producing a “pseudo-arcus,” mild hemolytic anemia, and progressive renal involvement. Enzyme deficiency causes high levels of LDL, leading to glomerular foam cells, which predominate in endothelial and mesangial cells. In addition, LCAT deficiency is responsible for low levels of serum cholesterol ester, a simple and reliable marker for diagnosis. Recurrence in renal allografts has been observed. Early systemic atherosclerotic changes may develop. The clinical presentation of lipoprotein glomerulopathy first described in 1989 by Saito et al. (9) is different. Lipoprotein deposition occurs within glomerular capillary lumina, forming voluminous thrombi consisting of lipid droplets, but it spares glomerular cells; there is type III hyperlipoproteinemia with apolipoprotein E abnormality; the renal disease is progressive and recurs in transplanted kidneys (10). The molecular mechanism of lipoprotein glomerulopathy has not been completely clarified.

**When to Consider a Genetic Cause of Renal Disease in Adults**

Progress in molecular genetics has deeply modified the classification of many genetic entities such as Alport syndrome and nephronophthisis-medullary cystic kidney disease complex. Whereas nephropediatricians are well aware of genetic diseases, adult nephrologists are often less attentive to them. Investigation of family history should not be omitted in the examination of every renal patient. The possibility of a genetic disease is schematically raised in two clinical situations.

**Positive Family History**

Positive family history is easily demonstrated in autosomal-dominant diseases with high penetrance such as ADPKD. However, in X-linked and autosomal-recessive diseases, the number of affected subjects may be very limited, and sometimes the proband is the first and only symptomatic member of the kindred. In X-linked diseases, female heterozygous carriers

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**Table 1. Comparison of data on birth prevalence (adapted from reference (3))**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Country (Years of Study)</th>
<th>Birth Prevalence per 10,000 Livebirths</th>
<th>Comments on Sources of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabry disease</td>
<td>Australia (1980 to 1996)</td>
<td>0.09</td>
<td>Reference laboratory data</td>
</tr>
<tr>
<td></td>
<td>The Netherlands (1970 to 1996)</td>
<td>0.02</td>
<td>Reference laboratory data</td>
</tr>
<tr>
<td></td>
<td>British Columbia, Canada (1972 to 1996)</td>
<td>0.03</td>
<td>Reference laboratory data</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>France, including Overseas Territories (1972 to 1994)</td>
<td>0.06</td>
<td>Newborn population-based survey</td>
</tr>
<tr>
<td></td>
<td>West Germany (1960 to 1979)</td>
<td>0.06</td>
<td>Newborn population-based survey</td>
</tr>
<tr>
<td></td>
<td>Denmark (1962 to 1971)</td>
<td>0.09</td>
<td>Newborn population-based survey</td>
</tr>
<tr>
<td></td>
<td>Australia (1980 to 1996)</td>
<td>0.04 (0.05*)</td>
<td>Reference laboratory data</td>
</tr>
<tr>
<td></td>
<td>British Columbia, Canada (1972 to 1996)</td>
<td>0.07 (0.08*)</td>
<td>Reference laboratory data</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>Finland (1963 to 1982)</td>
<td>0.13</td>
<td>Newborn population-based survey</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>Finland (1976 to 1993)</td>
<td>0.2</td>
<td>Newborn population-based survey</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>Denmark (1935 to 1953)</td>
<td>8.2 to 8.9</td>
<td>General population-based survey; equivalent of risk</td>
</tr>
<tr>
<td></td>
<td>United Kingdom, South and Mid-Wales (12/31/1989)</td>
<td>4.1</td>
<td>General population-based survey; equivalent of heterozygote frequency</td>
</tr>
<tr>
<td></td>
<td>France, Department of Cotes d’Armor (1988 to 1993)</td>
<td>9.0</td>
<td>General population-based survey; equivalent of heterozygote frequency</td>
</tr>
</tbody>
</table>

* If all births had occurred, i.e., in the absence of prenatal screening and termination of pregnancy.
can be asymptomatic or have limited abnormalities that can be missed or appear late in life. In the case of AFD, women can be severely affected (see Obrador et al. in this issue). In autosomal recessive diseases, heterozygotes are often asymptomatic. The consanguineous marriages, suggestive of recessive diseases, are rare in many countries. Most affected subjects with recessive conditions whose parents are unrelated are compound heterozygotes, with two different mutations of the same gene. A pattern simulating recessive inheritance, i.e., two or more siblings affected with no disorder in the parent, may occur in case of gonadal (germline) mosaicism. Mitochondrial disorders with renal involvement have emerged recently. They can originate from nuclear gene mutations or mitochondrial gene mutations. The first are inherited as other mendelian characters, whereas the second show unusual inheritance features; the condition can affect both sexes, but is passed only by affected mothers.

Of course, a negative family history does not exclude a genetic disease. Several factors may account for this. Family investigation may sometimes be complicated by the reluctance of some family members to cooperate, namely to provide information on parents, siblings, or offspring. False paternity is misleading (it can be recognized by DNA fingerprinting). De novo mutation may occur and explain the appearance of the disease in an individual who has no previous family history of the condition. The rate of de novo mutations differs from one genetic disease to another: low in ADPKD, high up to 60% of the cases in tuberous sclerosis. In X-linked Alport syndrome, it has been claimed to be approximately 15%.

The phenotypic expression of a genetic disease may be quite heterogeneous among various affected members of a given family carrying the same inherited mutation. Extensive study may be necessary to identify the carrier parent of tuberous sclerosis, with only very localized skin changes and/or asymptomatic intracranial calcifications. Such a variable expression from one family to another or even within a given family is found in dominant rather than recessive diseases and may be explained by environmental factors and modifier genes. Another explanation for this variability is somatic mosaicism. The mutation, not present in the germ line, appears later in the development of the zygote in some but not all cells. Consequently, the disease develops in some but not all tissues. This phenomenon has been demonstrated in tuberous sclerosis, von Hippel-Lindau disease, Lowe syndrome, and Alport syndrome [see references in reference 11]. In cases of germline mosaicism, apparently normal individuals may have multiple offspring with severe symptoms.

No Positive Family History, but the Disease Occurs in a Young Adult and Cannot Be Classified at First Glance

Nephrologists are often oriented by renal or extrarenal features. Obviously, the diagnosis of ADPKD cannot be missed by ultrasonography, but microcysts due to the glomerulocystic disease (another dominant disease) may be difficult to identify. The diagnosis of AFD may be first established on typical renal biopsy findings in a young adult, a not uncommon presentation. The presence of deafness suggests Alport syndrome, although hearing loss may be associated with renal disease in many other inherited disorders, such as AFD, branchio-oto-renal syndrome, Alström syndrome, hypoparathyroidism, mitochondrial cytopathies, etc. (12). Similarly, the occurrence of eye abnormalities detected by a systematic examination may orient toward a genetic disease: macular flecks to Alport syndrome, corneal opacities to LCAT deficiency, cornea verticillata to AFD. In addition, skin, nail or bone, etc. examination may reveal tuberous sclerosis, nail-patella syndrome, etc. Regarding rare diseases, consulting databases, such as ORPHANET (http://orphanet.infobiogen.fr) and Online Mendelian Inheritance in Man (OMIM: http://www.ncbi.nlm.nih.gov/omim/searchomim.html) or computer-assisted diagnosis can be rewarding.

One of the most important lessons for adult nephrologists is that rare inherited diseases, believed to be restricted to pediatric nephrology, may first reveal and be diagnosed in adults. Autosomal-recessive polycystic kidney disease or rare diseases, such as Alagille syndrome (cholestaticus due to paucity of intrahepatic bile ducts, butterfly vertebrae, congenital heart disease, and renal abnormalities in 20 to 30% of the cases) may progress to end-stage renal disease late in life (13,14). Renal involvement due to mitochondrial DNA mutations may first manifest in adults, in association with deafness, diabetes mellitus, maculopathy, and/or cardiomyopathy, mimicking therefore many other renal diseases. In an Australian report (5), the median age at diagnosis of AFD was 28.6 yr, ranging from 0.0 to 55.7 yr. In a heterozygous female, the diagnosis of AFD with heart and kidney involvement was first established at 74 yr of age (15). Indeed, renal disease has not been described in children with AFD; hence this disease will characteristically present first to the adult nephrologist.

Finally, it should be remembered that “well-classified” renal diseases, such as reflux nephropathy, are often familial, even though the genes involved are unidentified today, and that primary glomerular diseases, such as focal segmental glomerulosclerosis or IgA nephropathy, are often sporadic but may be familial, opening new avenues in research concerning the mechanisms of these diseases. In summary, nephrologists should consider genetic diseases that lead to end-stage renal failure, especially for genetic counseling in the families and for specific therapy if available.

References