Genetic kidney diseases in the elderly

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‘In my family, ever since ancient days, people have died so many times that death finally became hereditary’

Introduction

It may be provocative to introduce a report on inherited kidney diseases into a Symposium devoted to renal disease and ageing. Indeed, it is still believed that genetic diseases are restricted to children, and that genetics is related mainly to paediatrics. Our aim is to show that inherited, even monogenic, diseases often develop in adults, including elderly subjects. This is the case in Huntington’s disease, in Alzheimer’s disease, in most inherited forms of genetic amyloidosis, in most cases of von Hippel-Lindau disease, in non-insulin-dependent diabetes mellitus (which has a strong genetic component), in autosomal dominant polycystic kidney disease (ADPKD) and in many other adult-onset genetic diseases [1]. In these diseases, the first clinical manifestations often occur in adulthood, after 40 years of age or more.

Late progression in ADPKD

It has been well known for several decades that the mean age at end-stage renal disease (ESRD) in ADPKD patients is 55 years. About 20% of these patients progress to ESRD after 65 years of age [2]. From 1989 to 1996, 126 ADPKD patients reached end-stage at Necker Hospital, among whom 26 (20%) were 65 years of age or older, and five (4%) were 70 years of age or older (Table 1).

Epidemiological studies have established that renal failure in ADPKD is less progressive than previously thought. In the Olmsted County study, the diagnosis of ADPKD was made at autopsy in a significant number of cases, in patients who died at 80 years or older [3]. Other studies have shown in various population groups that 15–50% of ADPKD patients were not in ESRD by 70 years of age [2]. This diversity in the rate of progression explains why, in some instances, ADPKD is first discovered in the offspring rather than in the affected parent. There is, however, no systematic anticipation phenomenon in ADPKD families.

What are the main determinants of such a low rate of progression? The answer to this question is of great clinical interest since it may provide a means to slow the course of the disease. One of the main determinants of progression is the genetic type of ADPKD: on average, the age at ESRD is 70 years in PKD2 disease whereas it is 55 years in PKD1 disease (which represents 85% of the families with ADPKD). Both genes and their products have been identified. Both proteins interact [4,5]. This interaction results in an up-regulation of PKD1 but not PKD2. PKD1 may require the presence of PKD2 for stable expression [5]. It should be clear, however, that late and slow progression may be found in some PKD1 families and in some members of PKD1 families [2]. One may conceive that this might be explained by interaction of PKD2 or other modifying genes with PKD1 expression, and this interaction might depend on the PKD1 mutation and on the genetic environment. This example raises the crucial question as to what is the molecular mechanism of the late onset, what retards the expression of some inherited diseases whereas the defects often involve genes implicated in development, early in fetal life.

The gender of the patient is another factor involved in progression, the renal disease progressing more slowly in females than in males. This is exemplified in our recent series (Table 1): the higher the age at ESRD, the higher the percentage of women. All the five

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<th>Any age</th>
<th>126</th>
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<td>≥60 yr</td>
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<td>≥65 yr</td>
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<td>≥70 yr</td>
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Table 1. Age at ESRD in ADPKD, Hôpital Necker 1989–1996
patients aged 70 years or more were female. In addition, the rate of progression of renal failure is less rapid in elderly than in younger patients [6].

Extrarenal symptoms of ADPKD may first manifest in elderly patients. Although most cerebrovascular accidents in elderly ADPKD patients are of the ischaemic type, subarachnoid haemorrhage due to rupture of an intracranial aneurysm should also be considered. In the series collected by D. Chauveau et al., one patient with such an accident was 69 years of age [7].

**Late progression in X-linked dominant Alport’s syndrome**

In the adult-type X-linked Alport’s syndrome, the age at ESRD may range from 30 to 70 years of age. In one of these families in which the gene defect involving **COL4A5** has been demonstrated [8], a deaf male patient progressed to ESRD at 76 years of age. In more recent years, two affected male patients reached ESRD at 67 and 69 years, respectively. Such slow progression is common in the 10–15% of heterozygous females who progress to ESRD.

**Inherited disorders with renal involvement, presenting late in life**

The first example [9] deals with a 74-year-old woman who was referred to cardiology because of mitral regurgitation and congestive heart failure. Four years earlier, she had myocardial infarction and, 1 year earlier, a pacemaker was implanted. This woman also had renal disease with proteinuria and mild renal failure. Echocardiography showed marked biventricular hypertrophy, bialtrial enlargement and mild left ventricular dysfunction. There was no family history of cardiac or renal disease. It should be stressed that this is a common finding in X-linked or autosomal recessive disorders. The lack of positive family history does not exclude an inherited disorder.

Endomyocardial biopsy was performed: neither inflammation nor amyloidosis was detected. Electron microscopy study of this biopsy, however, was diagnostic, showing a distinctive population of myocytes containing lysosomes filled with lamellar deposits, typical of Fabry’s disease. The diagnosis subsequently was established by finding low α-galactosidase activity in leukocytes. This patient had no other abnormalities suggestive of Fabry’s disease. If renal biopsy had been performed, similar intralysosomal inclusions would have been documented in podocytes, responsible for urinary abnormalities [10].

The second example was reported in abstract form at the ERA-EDTA Congress by Jacquot et al. [11]. A 73-year-old woman was referred for advanced renal failure (serum creatinine concentration 339 µmol/l). She had several renal colics between 40 and 55 years of age with stone emission. Numerous crystals were found in the urine. These were identified as 2,8-dihydroxyadenine. Renal biopsy showed similar crystals in the interstitium and tubular cells and tubular lumens, in association with interstitial fibrosis. Adenine phosphoribosyl transferase (APRT) deficiency was documented in erythrocytes. This defect may lead to stones but also to ESRD as shown in other cases [12]. Thus, two rare inherited enzyme deficiencies, involving α-galactosidase A and APRT, respectively, were identified in elderly patients. The diagnostic of these metabolic diseases can be first made after 70 years of age.

Most genetic diseases exhibit a wide spectrum of severity and a wide range of ages at presenting symptoms. Von Hippel–Lindau (VHL) disease, an autosomal dominant disorder, illustrates this statement. Renal cell carcinoma at 62 years was the first manifestation in a woman belonging to a VHL family studied by D. Chauveau et al. [13]. Among 519 patients from the French VHL study group in whom age at diagnosis was known, VHL disease was first diagnosed in eight (1.5%) at 65 years of age or more. The revealing lesion was renal cell carcinoma (two cases), central nervous system haemangioblastoma (three case), retinal haemangioblastoma (two cases) and isolated renal cysts in one case in whom diagnosis was based on molecular genetics data. Of 317 living patients, 13 (4%) are >65 years of age; six of them have only a single localization of VHL disease (S. Richard et al., unpublished data).

Renal involvement in genetic amyloidosis may have a slow progression late in life [14]. In transthyretin-derived amyloidosis, polyneuropathy predominates in the Portuguese form characterized by the Met30 mutation. Renal amyloidosis is not uncommon in this form and can be responsible for ESRD late in life in some families [15]. In addition, the transthyretin Ile122 mutation is associated with cardiomyopathy. Surprisingly, this mutation is also responsible for ~25% of the cases of late-onset cardiac amyloidosis in black Americans whereas it is not found in whites [16]. Isolated cardiac amyloidosis is four times more common among blacks than whites in the US, and the high prevalence of the Ile122 mutation contributes to the increased frequency of senile cardiac amyloidosis among blacks.

Correct diagnosis of the inherited disorder in an elderly patient is of clinical relevance. It may lead to specific investigations (such as in VHL disease) or may affect the treatment (such as in cardiac amyloidosis where sensitivity to digoxin and calcium channel-blocking drugs is increased). In addition, correct diagnosis has consequences on the whole family: identification of the affected subjects, genetic counselling and/or specific therapy. Genetic renal diseases may be first diagnosed in elderly subjects. Nephrologists should be aware of and prepared for this possibility.

**References**

2. Pirson Y, Chauveau D, Grünfeld JP. Autosomal-dominant...