Ethics in renal genetics

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Ethical issues exist in all fields of Medicine –as in everyday life. However these issues are more sensitive in medical genetics for the following reasons; (i) recent progress in genetics has generated great hope among patients, some feelings of «triumph among geneticists, and some fear among citizens. How and when will treatment of genetic disorders be available? What are the needs, limits and dangers of genetic *screening* and of the so-called predictive medicine? (ii) Genetic diagnosis has two emotional and social consequences which go beyond «classical» individual medicine: it may have consequences on the potential offspring, that is on the life project of a given person. It may also have consequences on other members of the family, not only those who are affected but also those who are not affected and need reassurance.

I am not an expert in Ethics (and probably none exists). We are all confronted with ethical issues which we try to resolve by applying simple ethical principles and mainly, by sharing these issues with patients and families. Our main aim is to help people make their own decisions. Ethics cannot exist without information. The greatest danger in medical Ethics is dogmatism.

TRAINING NEPHROLOGISTS IN NEPHROGENETICS

The first ethical issue for nephrologists is to be adequately trained in genetics, not only in medical genetics at large, but also inherited kidney disorders. Genetics is not restricted to nephropediatrics. The most severe genetic diseases are diagnosed in children but the most common genetic diseases are seen in adults, such as autosomal dominant polycystic kidney disease (ADPKD).

In addition, adult nephrologists can be confronted with diseases which previously were thought to be restricted to children. This can be illustrated by many examples. Autosomal recessive PKD is usually diagnosed in children but approximately 50% of the children who reach 15 years of age are not in ESRD. In our experience, autosomal recessive PKD may progress to ESRD in adulthood between 20 and 55 years of age. In addition these patients also have congenital hepatic fibrosis, constantly associated with ARPKD and responsible for portal hypertension and/or dilatation of intrahepatic ducts. Adult nephrologists should be aware of these manifestations and know how to manage them. In other «pediatric» diseases, renal involvement may only appear unexpectedly in adolescence? young adulthood? This is due to the lengthy survival of these patients due to progress in pediatric and dietary care: for example, focal segmental glomerulosclerosis in type I glycogen storage disease, or progressive renal failure in methylmalonic acidemia or in Lowe syndrome.

Finally, mild forms of inherited disorders, usually revealed in children, may be initially diagnosed in adults. For instance, Alagille syndrome (characterized by paucity of intrahepatic bile ducts, pulmonary artery stenosis, and sometimes unilateral renal agenesis and renal artery abnormalities) may be recognized later in life and lead to ESRD between 40 to 50 years of age.

Managing these patients depends on an accurate diagnosis of the disease. In addition, these adults should receive adequate genetic counseling. Therefore, it is essential that all nephrologists have appropriate teaching and training in nephropediatrics and nephrogenetics.

GENETIC TESTING IN INHERITED KIDNEY DISEASES

Genetic testing must respect certain rules legally established in France (décret n° 2000-570, 23 juin 2000):

1. The tested person must give his/her written informed consent. Genetic testing is discouraged in children, except «if the child or his/her family can benefit personally from immediate preventive or curative measures». In von Hippel-Lindau, an autosomal dominant disease, children may develop retinal hemangioblastoma (responsible for blindness) early in life, or pheochromocytoma (responsible for severe paroxysmal hypertension). Genetic *screening* is advised in children at-risk, provided that parents give their informed consent.

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2. The Genetics Laboratory must deliver the results of the genetic test to the prescribing physician. The physician should then explain and transmit the results to the tested person. The results should not be transmitted directly to the tested person.

3. The «décret» and further directives encouraged partners in hospitals to create multidisciplinary groups, including namely nephropediatricians, adult nephrologists, geneticists, psychologists, specialized nurses, social workers etc. These groups are not only important for research, but also for promoting an integrated and coordinated approach in renal genetics, from childhood to adulthood, for the reasons mentioned above.

Education and information are key words in genetics. I have learned a great deal from patients and families, as well as from Associations or Foundations set up to support them. These structures are essential for the transfer of information and for establishing a fruitful dialogue.

Genetic testing may be of great clinical interest for identifying carrier females in X-linked disorders, such as in Alport syndrome or Fabry disease. Indeed some may be asymptomatic, others may have intermittent abnormalities (microhematuria), and other laboratory tests may be misleading (because of the random inactivation of one X-chromosome). Correct identification of heterozygous females is the first step in genetic counseling.

In autosomal recessive disorders, the main interest in genetic testing lies in antenatal diagnosis or more recently, in preimplantory diagnosis.

In autosomal dominant diseases, genetic testing may be clinically relevant in disorders such as VHL disease, where lesions develop progressively throughout the life cycle. Subjects at-risk can be tested. Only those carrying the mutation are submitted to regular follow-up and investigations. In contrast, in ADPKD, ultrasonography is a reliable and simple tool for diagnosis. Thus gene testing is not useful, except in a few cases (see E. Ars in this issue). The major point to stress (and to explain in genetic counseling) is that the detection of the mutation in some autosomal dominant diseases may not provide information on the expression, course and prognosis of the disease. Some subjects who carry the mutation may develop few phenotypic abnormalities, if any. By contrast however, even in the same family, others will develop a full-blown disease. Such a variable penetration can have multiple causes and mechanisms (modifier genes, environmental factors etc.). This clearly shows that in some cases, a genotypic lesion is insufficient for the complete clinical expression of the disease, and cannot alone account for the variable progression of the renal disease. Other factors are involved, and of course, should be taken into account in genetic counseling.

Jeffrey Lewis has proposed the following metaphor: «If the genome can be seen as a text or a script, then its phenotypic expression can be seen as a performance of that script, bringing the text to vibrant and unique life just as actors on a stage bring life to the words on a page.»

GENETIC COUNSELING

Many books and papers have been devoted to genetic counseling, and usually have been written by geneticists. I would just like to recall some of the general principles:

1. It is the physician's duty to inform the patient about the genetic nature of the disease; the patient or person at-risk has the right to know or not to know.

2. In my opinion, how to tell and how much to tell at a given time should be adapted according to each person (cultural background, level of education, emotional situation and so on).

3. The first goal of genetic counseling is to give information and to answer the questions raised by the patient or the person at-risk. That is the reason why genetic counseling should be shared by a nephrologist (who knows the natural history of the disease) and a geneticist (see below). Of course, genetic counseling is non-directive, it should be considered as a partnership, the patient or the at-risk subject makes her/his own decision. In complex cases it is essential to have a multidisciplinary approach with psychological support.

Antenatal diagnosis (or preimplantatory diagnosis) may be required by some parents in families affected by severe renal disease, such as nephropathic cystinosis, autosomal recessive PKD, Lowe syndrome, juvenile nephronophthisis etc. This has to be managed by qualified geneticists and psychologists. If need be, the nephrologist can be involved to provide information on the natural history of the disease. The first goal of antenatal diagnosis is to allow parents to have unaffected children.

Genetic counseling and antenatal diagnosis should be adapted to the therapeutic progress achieved. The recent introduction of enzyme replacement therapy will probably change the reactions of some patients with Fabry disease (provided that the hope placed in this treatment is confirmed in the future).

KIDNEY TRANSPLANTATION IN HEREDITARY RENAL DISEASES

I will focus on the ethical and medical issues concerning some inherited diseases raised by kidney donations from living relatives. In X-linked disease, the

first step is to correctly identify heterozygous females. Of course, some heterozygotes should be excluded from kidney donation in Alport syndrome (or in Fabry disease) because they have proteinuria and/or hypertension, and/or significant renal changes on biopsy. However we ignore the long-term risks of uninephrectomy in a heterozygous woman with Alport syndrome and isolated microhematuria, or in a heterozygous woman with Fabry disease and no urinary abnormalities. Kidney donations have been performed in the past in such circumstances in anecdotal cases with no significant deleterious effects. This possibility needs to be carefully and cautiously discussed with potential kidney donors. Today, it is impossible to propose a general statement relative to this matter.

In autosomal recessive diseases, heterozygotes are usually asymptomatic and kidney donations are usually accepted. This occurs mainly in nephropediatrics. We don't know, however, whether or not the long-term consequences of uninephrectomy are similar in all autosomal recessive kidney diseases.

Finally, in autosomal dominant diseases, the selection of the potential donors is generally easy in ADPKD. In contrast, it may be more difficult in diseases with incomplete penetration: which decision to make regarding a donor with branchio-oto-renal or nail-patella syndrome without renal involvement? What to do in a patient with inherited FSGS, carrying the α-actinin-4 mutation, but without urinary abnormalities? What advice to give to families with nephritis, deafness and giant platelets, in a potential donor who has only deafness and macrothrombocytopenia? The decision raises both medical and ethical issues. Ethics should not be separated from medicine, and should take into account the progress achieved progressively in medicine.

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