Podocin and Nephrotic Syndrome: Implications for the Clinician

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Idiopathic nephrotic syndrome (INS) is the most frequent glomerular disease in childhood. Most of the children respond to corticosteroid therapy whereas 10% of them fail to respond to this treatment. They are at risk of extrarenal complications of the nephrotic syndrome and may develop end-stage renal disease, which occurs in up to 50% of white children after a follow-up of 5 yr and 80% of African-American children after a follow-up of 3 yr. Steroid-resistant INS accounts for more than 10% of children who progress to end-stage renal disease. Attempts to find treatments that could induce a remission and thus prevent the progression of the disease have not been conclusive. One of the possible reasons why the interpretation of the results of different therapeutic trials is difficult is that there are several disease entities under the denomination of steroid-resistant INS or primary focal and segmental glomerular sclerosis (FSGS). Indeed, during the past few years, the progresses in molecular genetics have allowed the discovery of several genes that are involved in the pathogenesis of INS (1,2).

In 1995, Antignac’s group (3) mapped a locus to chromosome 1q25-q31 for autosomal recessive INS characterized by an early onset, minimal changes, or focal and segmental glomerulosclerosis on initial renal biopsy, steroid resistance, rapid progression to renal failure, and no recurrence after renal transplantation. In 2000, using a positional cloning approach, the same group (4) identified the causative gene, NPHS2, which is only expressed on podocytes and encodes podocin, a lipid raft-associated protein at the filtration slit. By immunoelectron microscopy, podocin is located at the foot processes (5). Podocin has been shown to recruit nephrin in the lipid raft microdomains, which is necessary for the proper initiation of nephrin signaling (6). Podocin also interacts with CD2AP in lipid rafts (7). These data suggest that podocin is important for the structural organization of the slit diaphragm. More than 30 different NPHS2 mutations, comprising nonsense, frameshift, and missense mutations, were found to segregate with the disease. The R138Q substitution is the most frequent, probably due to a founder effect in northern Europe. The R138Q mutant podocin is retained in the endoplasmic reticulum and loses its ability to recruit nephrin in the lipid rafts (6). Tsukaguchi et al. (8) studied 30 families with adolescent or adult onset FSGS with apparent autosomal recessive inheritance. NPHS2 mutations appeared to be responsible for the disease in nine of these families. They found different mutations than those observed in the early-onset form, suggesting that podocin may retain some function in these patients. Interestingly, in six families, affected individuals were compound heterozygous for a R229Q variant. The R229Q podocin was shown to have a decreased binding to nephrin. From these observations, it can be concluded that the severity of the disease caused by NPHS2 mutations is variable. For example, podocin mutants that are retained in the endoplasmic reticulum are associated with earlier onset of the disease than those correctly targeted to the cell membrane (9).

As patients with NPHS2 mutations and INS have a recessive disease, in most families with few sibships, the disease will affect only one child. For this reason, podocin mutations have been looked for in patients with the sporadic form of steroid-resistant INS. Not surprisingly, mutations were identified in 15 to 30% of such patients (10,11). Ruf et al. (12) further extend and confirm these findings. The authors studied a total of 152 patients with sporadic FSGS and found podocin mutations in 32 of them (21%).

Ruf et al. found no podocin mutations in 124 children with steroid-sensitive INS (12), confirming the results of Caridi et al. (13) and Frishberg et al. (11) and demonstrating that NPHS2 mutations are restricted to steroid-resistant INS. The authors suggest that children with a first episode of nephrotic syndrome should be tested for podocin mutation before therapy to avoid an unnecessary steroid course in those with NPHS2 mutations. Considering that 85% of children with INS are steroid-responsive and that podocin mutations are found in only 20% of steroid-resistant patients, one may argue that mutations will be found in fewer than 5% of cases. Moreover, this determination may delay the start of steroid therapy and thus expose the patient to the complications of the nephrotic syndrome. The only exception would be those patients with a familial history of steroid-resistant INS and documented mutations of the podocin gene as reported by Frishberg et al. (11).

Conversely, in patients with steroid-resistant INS, the identification of NPHS2 mutations in a sporadic form of the disease is of importance for therapeutic considerations as well as for genetic counseling. Ruf et al. (12) have data on the results of treatment in 29 patients with podocin mutations. None of them had a complete response to cyclosporine or cyclophosphamide. The significance of the partial response observed in five pa-
tients is questionable, as a decrease of proteinuria with cyclosporine therapy may be secondary to a decrease in GFR. Therefore, as there are no clinical characteristics, except steroid resistance, that can predict NPHS2 mutations in an individual patient, it can be proposed to test steroid-resistant patients for podocin mutations before further therapy.

Pediatric nephrologists are often faced with the choice of therapy in children with steroid-resistant INS. There have been many recent discussions on possible therapeutic trials, especially in the United States and in Europe. Knowing that in a subset of patients, the disease is secondary to NPHS2 mutations and that the response to any form of therapy may be different from that of patients without mutations, it would not be advisable to start a trial without identifying those with podocin mutations before enrolling the patients. Moreover, the proportion of patients with mutations of glomerular proteins responsible for steroid-resistant INS is certainly higher, as genetic heterogeneity has been found in autosomic recessive forms of the disease (3).

In patients with steroid-resistant INS and progression to renal failure, the clinician is faced with the risk of recurrence, which most often occurs within the first 48 h after transplantation. The rate of recurrence is estimated to be around 30%. In children, recurrence is more frequent when the disease has started after 6 yr of age. A rapid progression to renal failure is another factor associated with recurrence. Patients with mesangial proliferation on initial renal biopsy are at high risk of recurrence. There is strong evidence that circulating permeability factors are involved, especially when recurrence occurs shortly after transplantation.

None of the children with familial steroid-resistant INS described by Boute et al. (4) had recurrence after transplantation. However, the number of patients with NPHS2 mutations who were transplanted was limited and no definite conclusion could be made, although one can assume that circulating factors are not involved in the pathogenesis of INS in patients with a molecular defect of a podocyte protein. Bertelli et al. (14) reported a 38% rate of recurrence in patients with podocin mutations. However, only two of the five patients with recurrence of proteinuria had a renal biopsy. Moreover, only two of the five patients with proteinuria had homozygous mutations, whereas the other three had heterozygous missense mutations involving only one allele. These mutations may represent variants. One of the two patients with homozygous mutations had a rapid disappearance of proteinuria after plasma exchanges, and no renal biopsy specimen was available. Interestingly, Ruf et al. (12) found a very low rate of recurrence in patients with podocin mutations. Indeed, only 2 (8%) of 24 patients with homozygous or compound heterozygous mutations experienced recurrence of proteinuria, which unfortunately was not well documented. These findings tend to support the fact that the risk of recurrence is very low in patients with podocin mutations.

From these results, Ruf et al. (12) conclude that living related donor transplantation might be considered more readily. This assumption merits a word of caution if the donor is a parent with a heterozygous NPHS2 mutation. At present, the significance of single heterozygous mutations is unknown, and it is possible that other factors, genetic or environmental, are involved in the susceptibility to develop FSGS. Therefore, the kidney from a relative who is heterozygous may be more susceptible for the long-term development of FSGS and the living donor with one kidney may be at risk of FSGS. This word of caution is supported by a recent report (15). Mice lacking CD2AP develop congenital nephrotic syndrome and die shortly after birth. Kim et al. (15) found that CD2AP heterozygous mice have reduced concentrations of CD2AP protein and develop glomerular changes at 9 mo similar to human FSGS. Moreover, the authors found two African-American patients with FSGS who had a heterozygous mutation of the CD2AP gene, suggesting that CD2AP haploinsufficiency is linked to FSGS susceptibility.

References
11. Frishberg Y, Rinat C, Megged O, Shapira E, Feinstein S, Raas-Rothschild A: Mutations in NPHS2 encoding podocin are a


