Anti-nephrin antibodies in primary podocytopathies

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Damage to podocytes, which are cells playing a central role in the filtering process of the kidney, leads to pronounced loss of protein into the urine. This can result in progressive loss of renal function, including the need for renal replacement therapy, or other life-threatening complications such as pulmonary embolism (blood clots in the lung). Minimal change disease and primary focal segmental glomerulosclerosis are among the most common causes of autoimmune-mediated podocyte damage. The exact mechanism by which these two diseases damage podocytes remains unclear.

Recently, an antibody against components of podocytes (anti-nephrin antibody) was discovered as a possible cause for the development of minimal change disease. Also, punctate changes in immunofluorescence, a special histological staining technique of kidney biopsy specimens, have been identified, which have rarely been described in the literature. In primary focal segmental glomerulosclerosis, a pathogenic circulating factor has been proposed as etiology as well. This theory is supported by the fact that therapeutic removal of blood plasma, which potentially removes this pathogenic circulating factor, reduces protein loss into the urine in selected patients with recurrent primary focal segmental glomerulosclerosis after kidney transplantation. Moreover, plasma that was removed from patients with recurrent primary focal segmental glomerulosclerosis after kidney transplantation induced protein loss into the urine when injected into rats.

We now plan to confirm these newly discovered anti-nephrin antibodies as well as the newliy described histological changes in our patients with minimal change disease, and additionally identify them in primary focal segmental glomerulosclerosis. For this purpose, we will identify patients who have been diagnosed with either of these diseases by renal biopsy at our institution since 2005. We will reexamine the existing kidney biopsy specimens by immunofluorescence microscopically for these newly discovered changes. In addition, we will examine blood samples still available in blood banks from these patients with regard to anti-nephrin antibodies. As controls, we will look for anti-nephrin antibodies in blood samples from healthy patients and from patients with other kidney diseases. As a primary endpoint, we have chosen the percentage of patients who have the anti-nephrin antibody or the punctate changes in immunofluorescence.

If we confirm anti-nephrin antibodies in minimal change disease and newly discover them in primary focal segmental glomerulosclerosis, we can assume that these are not two different diseases but in fact the same disease of different degree of severity, which would be a paradigm shift. The anti-nephrin antibodies, similar to the anti-PLA2R antibodies in membranous glomerulonephritis, could at best replace renal biopsy, an invasive examination with a significantly increased bleeding risk, in establishing the diagnosis. The presence of anti-nephrin antibodies could also influence therapy by favoring regimens that inhibit antibody formation, thus allowing more targeted and presumably more effective therapy. In addition, the antibody could be used to monitor therapeutic response or to assess prognosis, for example, prior to transplantation. Confirmation of the punctate changes in immunofluorescence would replace the current doctrine that immunofluorescence is unremarkable in minimal change disease.

Thus, our project has a potentially far-reaching benefit in terms of disease understanding but also in terms of diagnosis and therapy, which could reduce patient suffering and improve prognosis.