Trimarchi H. J Rare Dis Res & Treatment. (2016) 1(2): 32-33
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Journal of Rare Diseases Research & Treatment

Commentary Open Access

Podocyturia as a biomarker of early kidney damage in fabry nephropathy

Commentary: Podocyturia is significantly elevated in untreated vs treated Fabry adult patients[1]

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Article Info

Article Notes
Received: August 02, 2016
Accepted: September 06 , 2016

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Glomerular involvement is invariably present in the progression of kidney disease, regardless of the etiology under consideration. Human beings are born with a determined number of glomeruli, which decrease in number along lifetime. Within each glomerulus, there exist approximately 500 podocytes[2]. These epithelial cells compose to visceral layer of Bowman's capsule, and present several interesting characteristics. Podocytes are unable to undergo mitosis and cellular division under normal circumstances, form part of the glomerular filtration barrier, synthesize components of the glomerular basement membrane and secrete vascular endothelial growth factor, a critical component that contribute to the health of the fenestrated endothelium. Even in normal conditions, podocytes are lost in the urine, a phenomenon known as podocyturia. This irreversible detachment leads to glomerular sclerosis and obliteration when approximately 40% of each glomerular podocyte population is lost[3]. This podocyte loss precedes the appearance of proteinuria, another marker of kidney disease. Therefore, the identification of a podocyte loss above normal levels in patients with normal renal function and without proteinuria may alert physicians to investigate a probable glomerular involvement at early subclincal stages.

Fabry disease is an ideal situation to assess the utility of podocyturia. Being an X-linked hereditary entity, once an index case is diagnosed, all relatives are called to be tested for the activity of the mutated enzyme, α-galactosidase A, before proteinuria appears. Many of the relatives, particularly the young, are asymptomatic,or may present mild symptoms of the disease. Despite specific therapy for Fabry disease exists, Fabry nephropathy progresses at a slower rate when compared to untreated cases, and eventually ends up in dialysis at the age of 40 to 50 years[4].

In our methodological lines of research, we employ synaptopodin as a marker of podocytes. The search for podocytes in the urine is time-consuming. Briefly, a mid-stream freshly voided urine sample is collected on-site after a minimum of 3 h without voiding; 20 ml of urine is centrifuged at 700g for 5 min using a cytospin; the supernatant is discarded and the obtained sediment stored in 100 µl aliquots at room temperatura mixed with a 1.5 ml solution made of 40 % paraformaldehyde diluted in phosphate-

buffered saline (PBS) (pH 7.2–7.4) to reach a final 10% concentration. Nuclei of podocytes are then stained with 40,6-diamidino-2-phenylindole. Podocytes are finally identified by immunofluorescence using synaptopodin as the primary antibody. Samples are analyzed employing an epifluorescent microscope. Following our standardized technique, podocytes are to be counted in 10 randomly chosen 20X fields of the slides and the average of the counted podocytes in the microscopy fields is considered as the final count for each subject. The results are corrected based on the levels of urinary creatinine found in each sample.

We have recently assessed podocyturia, in 30 controls and in Fabry patients with (n=18) and without (n=19) enzyme therapy, correlating podocyturia with proteinuria and renal function in a cross-sectional study. We found that patients with Fabry disease displayed heavier podocyturia than controls. Moreover, untreated individuals presented significantly higher podocyturia, lower proteinuria and better renal function than those who were treated. These findings support other reports which suggest that enzyme replacement therapy may be started at advanced stages of the disease. We finally propose that podocyturia may antedate proteinuria. It would be compelling to assess whether enzyme replacement therapy may protect against podocyte loss.

Our paper presents several limitations. We suggest that podocyturia could be employed to assess the early degree of kidney damage despite the absence of proteinuria and for follow-up purposes. However, while the technique is non-invasive and simple, it is- as mentioned above- time-consuming. Moreover, it needs to be validated with studies adjusted for kidney function, age and probably also to the type of glomerulopathy, among other variables. In our study, only one marker was employed to identify podocytes, but certainly the addition of other podocyte markers could have identified podocytes at other cell-cycle stages. All these considerations underscore the need to standardize the study of podocyturia. Ours was a cross-sectional study, but the effectiveness of therapy and the evolution of podocyturia, proteinuria and renal function in all patients requires a longitudinal follow-up. Being Fabry disease a genetic entity, the impact of the different mutations on kidney function is a relevant factor that was not analyzed ad-hoc in this study with respect to podocyturia. Nevertheless, all these mutations included in our study were related to the classical phenotype and not to late-onset variants of the disease. Finally, our study was performed with the only approved treatment for Fabry disease: enzyme replacement therapy. It will certainly be interesting and challenging to assess podocyturia levels in patients with forthcoming therapies, as migalastat, a chaperone. This pharmacological strategy is based on a molecule that restores the activity of certain mutant forms of α-galactosidase A. Migalastat has just been approved for the treatment of some patients with Fabry disease[5]. Considering the fact that Fabry disease is a rare entity, we have included a relatively large number of subjects employing the same drug and dose, and the promising results of our study compel us to continue our investigations.

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