LETTER TO THE EDITOR
Iran J Allergy Asthma Immunol
April 2014; 13(2):144-146.

Current Concepts on Anti-Phospholipase A2 Receptor Antibody in Idiopathic Membranous Nephropathy

Hamid Nasri

Department of Nephrology, Division of Nephropathology,
Isfahan University of Medical Sciences, Isfahan, Iran

Received: 2 May 2013; Accepted: 2 June 2013

Keywords: Membranous nephropathy, Nephrotic syndrome, Phospholipase A2 receptor

The most common cause of nephrotic syndrome in adults is idiopathic membranous nephropathy, which is an antibody-mediated autoimmune glomerular disease.[1-3] Membranous glomerulopathy can be secondary to autoimmune diseases, various infections, drugs and malignancies.[1-5] In idiopathic membranous nephropathy (IMN), disease can be developed due to the binding of a circulating antibody to an antigen that is presented on podocytes.[2-6] However, in secondary forms of membranous nephropathy, the subepithelial deposits may arose from deposition of circulating immune complexes along the capillary walls or from binding of antibodies to antigens that are originated from the tumor and were implanted in the basement membrane.[1,3,5,7] Patients with membranous glomerulopathy are presented with a broad range of urine protein excretion. However, the amount of proteinuria often fails to correlate with the quantity of immune deposits, demonstrable on fluorescent and electron microscopy.[1,3,5,7] Currently, several therapeutic options are available, however, in some cases IMN spontaneous remission may happen.[3,5,7] Nonetheless, in a substantial number of patients the response to treatment is poor and the risk of renal disease development remains high. It was found that IMN may lead to end-stage kidney failure among 40–50% of adult patients in long term.[3,5,7-10]

The prediction of the disease intensely correlates with the remission rate of the patients.[3,5,7] Age, kidney function, proteinuria and gender of patients can be considered to describe individuals at risk.[3,5,7] However, these mentioned predictors may not be relevant predictors for the spontaneous course or predictors of outcome or the potential necessity to intensify the immunosuppressive therapy of the disease.[3,7] In fact, in some patients with large proteinuria, spontaneous remission may occur in up to 20–25% of cases,[3,5,7] hence, a predictor for disease evolvement and/or treatment effects would be a very useful tool for therapy decisions of membranous nephropathy. Therefore, prognostic markers in IMN would help clinicians to recognize potential candidates to speedy intervention and specific strategies. Generally, the development of biomarkers largely depends on the knowledge of the disease pathogenesis. In IMN, serologic diagnosis has been elusive because the target antigen is unidentified for several years. It has become evident that binding of circulating autoantibodies to target antigens on the podocyte will start the disease process.[5,11,12] Up to now, a significant amount of efforts have been paid to identify the target antigens of IMN.[5,11,12] Previously, studies of membranous nephropathy in a rat model namely Heymann's nephritis, proved that the subepithelial immune deposits containing of the target antigen, megalin, with circulating antimegalin antibodies are formed in situ.[1,3,7,11] However, megalin is not expressed on human podocytes and is not the target antigen in human disease.[1,3,7,11] Recently, new podocyte autoantigens have been detected and investigations is now focused on the development and authentication of a panel of

Corresponding Author: Hamid Nasri, MD;
Department of Nephrology, Division of Nephropathology, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: (+98 311) 220 8081, Fax: (+98 311) 223 5043, E-mail: hamidnasri@med.mui.ac.ir

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

antibodies to risk stratify patients and support clinical decision making. A minimum of four autoantigens have been found. One of them, the phospholipase A2 receptor, is normally expressed in podocyte membrane.[12,13] In fact the phospholipase A2 receptor (PLA2R) is a type I transmembrane glycoprotein related to the C-type animal lectin family such as the mannose receptor. PLA2R regulates a number of biological responses produced by secretory phospholipase A2s (sPLA2s).[14,15] It was suggested that group of IB sPLA2 /PLA2R pathway had a potential role in the production of pro-inflammatory cytokines. Also, PLA2R has been found to be involved in the clearance of sPLA2s.[16] Therefore, determining anti-PLA2R serum levels in patients with nephrotic syndrome should designate a probable diagnosis of IMN and in patients in which IMN had a pathology confirmation may be a determining factor to exclude secondary forms of the disease.[14-16] Moreover, anti-PLA2R may be used as a marker of response to treatment.[15-17] Thus, the recent finding on phospholipase-A_2-receptor antibodies (PLA_2R-Ab) may have a role in the progress of primary membranous glomerulonephritis and suggest the opportunity to measure a marker to help diagnosis, classify and finally monitor the course and outcome of patients with IMN.[15-17] However, the finding of autoantibodies to M-type phospholipase A2 receptor in IMN still evokes a question as to whether they are truly pathogenic. It is evident that IMN is an IgG4 dominant disease, in which antibodies against PLA2R were mainly of the IgG4.[16-18] However, IgG4 is not binding complement, this has triggered the debate on the pathogenic role of these antibodies. The recent study was suggested that PLA2R- IgG4 may bind mannose binding lectin, and thus activates complement via the mannose binding lectin pathway.[6,15,18] While, several authors have measured the occurrence of anti-PLA2R antibodies in patients with secondary MN, thus more data are still required before we can safely conclude that the presence of anti-PLA2R antibodies always reveals IMN and precludes the need to investigate for an underlying cause.[15-19] Since PLA2R antibodies have not been identified in healthy controls and also proteinuria due to other glomerular diseases like, focal segmental glomerulosclerosis, IgA nephropathy or minimal change nephropathy, was associated with negative PLA2R antibodies, however, the numbers of publications in the literature are small and it still needs further investigation.[16-20] Measurement of anti-PLA2R is now commercially available to use and assay, hence, we suggest to store serum samples reserved at baseline and during follow-up. This would permit to perform measurements at a time point when all questions regarding the efficacy of anti-PLA2R antibody measuring in patients with idiopathic membranous nephropathy is fully resolved. We believe that it is too immediate to discard a kidney biopsy in patients with nephrotic syndrome. Indeed, recent studies further doubted the role of serum anti-PLA2R as the main pathogenic antibody in IMN. In this regard, we are enthusiastically awaiting the development of more precise assay of anti-PLA2R antibody.

REFERENCES

1. Oh YJ, Yang SH, Kim DK, Kang SW, Kim YS.Autoantibodies against phospholipase A2 receptor in Korean patients with membranous nephropathy. PLoS One 2013; 8(4):e62151.
2. Seif EI, Ibrahim EA, El hefnawy NG, Salman MI. Histological patterns of idiopathic steroid resistant nephrotic syndrome in Egyptian children: A single centre study. J Nephropathol 2013; 2(1):53-60.
3. Glassock RJ. Diagnosis and natural course of membranous nephropathy. Semin Nephrol 2003; 23(4):324-32.
4. Nasri H, Ardalan MR. Significance of hyperuricemia in immunoglobulin A nephropathy. J Ren Inj Prev 2013; 2(3): 105-106.
5. Murtas C, Ravani P, Ghiggeri GM. New insights into membranous glomerulonephritis: from bench to bedside. Nephrol Dial Transplant 2011; 26(8):2428-30.
6. Rolla D, Bellino D, Peloso GC, Rastaldi MP, Simonini P, Ravetti. The first case of IgG4-related disease in Italy. J Nephropathol 2013; 2(2):144-9.
7. Stone JH. IgG4: a tantalizing link between causes of membranous glomerulonephritis and systemic disease. Kidney Int 2013; 83(3):348-50.
8. Nasri H. Antiphospholipid syndrome-associated nephropathy: Current concepts. J Ren Inj Prev 2013; 2(1): 1-2.
9. Nasri H, Mubarak M. Contrast induced nephropathy has to be differentiated from kidney injury due to atheroembolic disease. J Ren Inj Prev 2013; 2(3):107-8.
10. Kari J. Epidemiology of chronic kidney disease in children. J Nephropathol 2012; 1(3):162-3.
11. Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009; 361(1):11–21.
12. Ardalan MR, Ghafari A, Hamzavi F, Nasri H, Baradaran B, Majidi J. Antiphospholipase A2 receptor antibody in idiopathic membranous nephropathy: A report from Iranian population. J Nephropathol 2013; 2(4):241-8.

13. Lv J, Hou W, Zhou X, Liu G, Zhou F, Zhao N,et al.Interaction between PLA2R1 and HLA-DQA1 Variants Associates with Anti-PLA2R Antibodies and Membranous Nephropathy. J Am Soc Nephrol 2013; 24(8):1323-9.
14. Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009; 361(1):11-21.
15. Nayer A, Asif A. Idiopathic membranous nephropathy and anti-phospholipase A2 receptor antibodies. J Nephropathol 2013; 2(4): 214-6.
16. Malleshappa P. C1q nephropathy- unity in diversity. J Ren Inj Prev 2013; 2(4): 117-118.
17. Hofstra JM, Beck LH Jr, Beck DM, Wetzels JF, Salant DJ. Anti-phospholipase A_2 receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2011; 6(6):1286-91.
18. Nasri H, Mubarak M. Sudden deterioration of renal function in a patient with nephrotic syndrome and a very high hepatitis B viral DNA load. J Ren Inj Prev 2012; 1(1):39-41.
19. Debiec H, Martin L, Jouanneau C, Dautin G, Mesnard L, Rondeau E, et al. Autoantibodies specific for the phospholipase A2 receptor in recurrent and De Novo membranous nephropathy. Am J Transplant 2011; 11(10):2144-52.
20. Qin W, Beck LH Jr, Zeng C, Chen Z, Li S, Zuo K. Anti-phospholipase A2 receptor antibody in membranous nephropathy. J Am Soc Nephrol 2011; 22(6):1137-43.