Deciphering the Autoimmune Pathogenesis in Fibrillary Glomerulonephritis: The Story is not yet Complete

Fibrillary glomerulonephritis (FGN) is a rare group of glomerular diseases characterized by the deposition of periodic acid–Schiff–positive and Congo red–negative fibrillary material in the glomeruli.[1,2] The disease has both fascinated and confused the nephrologists and nephropathologists alike for several reasons, including its elusive nature, its pathogenesis, diagnosis, treatment, and last, but not the least, its relationship with a closely related condition of immunotactoid glomerulopathy. Kidney biopsy is the only definitive method for making its diagnosis, and till recent past, its diagnosis could only be made on electron microscopic (EM) study of kidney biopsy, a modality not readily available in many parts of the world, especially in developing countries. No sensitive or specific biomarker was available for its early and accurate diagnosis.[1,2] However, in early 2018, two independent research groups from the Mayo Clinic in Rochester, Minnesota, and from the University of Washington in Seattle almost simultaneously reported a novel protein marker, DnaJ homolog subfamily B member 9 (DNAJB9), which was found in relative abundance in the glomeruli of patients with FGN, for sensitive and specific diagnosis of FGN by immunohistochemistry (IHC).[3,4]

The protein was isolated from the glomeruli of FGN cases by a relatively novel technique for use in the investigation of glomerular diseases, that is, laser capture microdissection followed by proteomic analysis by mass spectrometry (MS). Subsequently, antibodies were raised against this protein and tested by immunofluorescence and IHC techniques for localization of the protein in the glomeruli. Co-localization was demonstrated with immunoglobulin G (IgG; later found to be belonging to IgG4 and IgG1 subtypes, with the former being predominant) and classical pathway complement components suggesting the formation of immune complexes.[3,4] Thus, FGN may be considered as an autoimmune disease, in which antibodies against the putative autoantigen, DNAJB9, are formed resulting in immune complex formation and deposition in the glomeruli. Although this discovery may be considered a breakthrough in the diagnosis of FGN, there are still many more questions than answers for this disease, such as what triggers the formation of autoantibodies, whether immune complexes are formed in the glomeruli or are deposited from the circulation, whether DNAJB9 is a mediator of kidney damage in FGN, or an innocent bystander, and so on.

The marker itself has several potential advantages; it is easy to perform, cost-effective, readily available, and quick – these are all relative to the EM study. An added advantage is that the test can be performed on paraffin-embedded tissue by IHC. Clearly, one other major advantage is that it obviates the need for EM study for a definite diagnosis of FGN.

There is as yet no published study on the diagnostic utility of this marker from South Asian region. EM facility is available in only few select centers in this region.[5] This implies that the disease is still probably underdiagnosed in this part of the world. We may be missing some cases of congophilic FGN, a recently reported entity, which can easily be misdiagnosed as amyloidosis.[6]

More recently, Nasr *et al*.[7] investigated the possibility of using serum DNAJB9 levels as a potential diagnostic marker and detected a fourfold higher level of serum DNAJB9 in FGN patients compared with controls, including patients with other glomerular diseases. They also found that serum DNAJB9 levels negatively correlated with the estimated glomerular filtration rate in patients with FGN. They concluded that serum DNAJB9 levels accurately predict FGN with moderate sensitivity (67%) and with high specificity (98%) with very high PPV and NPV (89% and 95%, respectively). A receiver operating curve analysis demonstrated an area under the curve (AUC) of 0.958, which proves its diagnostic utility. These results suggest that serum DNAJB9 could be a valuable marker to predict FGN, particularly in complementing kidney biopsy for the diagnosis of FGN.[7,8]

The discovery of DNAJB9 has also paved the way for future prospects of the development of targeted therapy for FGN, for which currently no specific treatment is available.

In conclusion, DNAJB9 is a potentially valuable IHC marker for accurate diagnosis of FGN, but further research is clearly indicated to fully understand this elusive disease and specifically to develop specific targeted therapy.

Muhammed Mubarak

Department of Histopathology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan

Address for correspondence:
Dr. Muhammed Mubarak,
Professor of Pathology and Head of Department, Histopathology Department, Sindh Institute of Urology and Transplantation, Karachi - 742 00, Pakistan.
E-mail: drmubaraksiut@yahoo.com

References

1. Rosenstock JL, Markowitz GS. Fibrillary glomerulonephritis: An update. Kidney Int Rep 2019;4:917-22.
2. Nasr SH, Fogo AB. New developments in the diagnosis of fibrillary glomerulonephritis. Kidney Int 2019;96:581-92.

3. Desari S, Alexander M, Vrana J, Theis J, Mills J, Negron V, *et al*. DnaJ heat shock protein family member B9isabiomarkerfor fibrillary GN. J Am Soc Nephrol 2018;29:51-6.
4. Andeen N, Yang H-Y, Dai D-F, Maccoss M, Smith K. DNAJ homolog subfamily B member 9 is a putative autoantigen in fibrillary glomerulonephritis. J Am Soc Nephrol 2018;29:231-9.
5. Mubarak M, Kazi JI. Role of immunofluorescence and electron microscopy in the evaluation of renal biopsies in nephrotic syndrome in a developing country. Ultrastruct Pathol. 2009 Dec; 33 (6):260-4.
6. Alexander MP, Dasari S, Vrana JA, Riopel J, Valeri AM, Markowitz GS, *et al*. Congophilic fibrillary glomerulonephritis: A case series. Am J Kidney Dis 2018;72:325-36.
7. Nasr SH, Dasari S, Lieske JC, Benson LM, Vanderboom PM, Holtz-Heppelmann CJ, *et al*. Serum levels of DNAJB9 are elevated in fibrillary glomerulonephritis patients. Kidney Int 2019;95:1269-72.
8. Andeen NK. Elevated serum concentrations of DNAJB9 in fibrillary glomerulonephritis: Another step toward understanding a progressive disease. Kidney Int 2019;95:1025-6.

Access this article online

Quick Response Code:

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_293_20

How to cite this article: Mubarak M. Deciphering the autoimmune pathogenesis in fibrillary glomerulonephritis: The story is not yet complete. Indian J Nephrol 2022;31:195-6.

Received: 21-06-2020; **Revised:** 08-09-2020; **Accepted:** 06-07-2021; **Published:** 13-11-2021