

The Importance of Immunohistochemical Staining with DNAJB9 for the Diagnosis of Fibrillar Glomerulonephritis



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Abstract

Fibrillary Glomerulonephritis (FGN) is a rare glomerulopathy, corresponding to less than 1% of all renal biopsies performed. The pathogenesis mechanisms of FGN are still not completely understood and most cases are considered idiopathic. The clinical presentation is characterized by proteinuria, hematuria, arterial hypertension and renal failure. The evaluation of FGN is a diagnostic challenge in the practice of the pathologist, because there are no morphological characteristics with highly specific or pathognomonic lesion. The use of a sensitive and specific biomarker can make an important contribution to renal pathology and the differential diagnosis of diseases with fibrillar deposits. In this context, DNAJB9 can be investigated by immunohistochemical technique and is useful for the diagnostic definition of FGN.

Keywords: DNAJB9, Biomarker, Immunohistochemistry, Kidney, Fibrillary GN

Abbreviations: FGN: Fibrillary Glomerulonephritis; LM: light microscopy; IF: immunofluorescence; EM: electron microscopy

Introduction

What is Fibrillary Glomerulonephritis?

Fibrillary Glomerulonephritis (FGN) is a rare glomerulopathy, corresponding to less than 1% of all renal biopsies performed [1]. This entity was first described by Rosenmann and Eliakim in 1977, who reported a patient with nephrotic syndrome who identified a glomerular deposition of amorphous material, which resembled amyloid by light microscopy, but their fibrils shorter than amyloid fibrils in ultrastructural analysis [2]. However, it was only in 1983 that FGN was defined as a distinct glomerular disease [3]. The pathogenesis mechanisms of FGN are still not completely understood and most cases are considered idiopathic [1,4-7]. Approximately one third of the cases, an etiological association is found with malignant neoplasms, dysproteinemia, hepatitis C and autoimmune diseases [7,8]. The clinical presentation is characterized by proteinuria (100%), hematuria (~ 50%), systemic arterial hypertension (~70%) and renal failure [5-7]. Renal survival is poor, with almost 50% progression to end-stage renal disease within 4 years; however, with good patient survival, being 80% at 4 years of follow-up [7]. In addition, because there is no effective therapy, a recurrence rate after a kidney allografts variable between 35-50% [9].

How is a Fibrillary Glomerulonephritis Diagnosed?

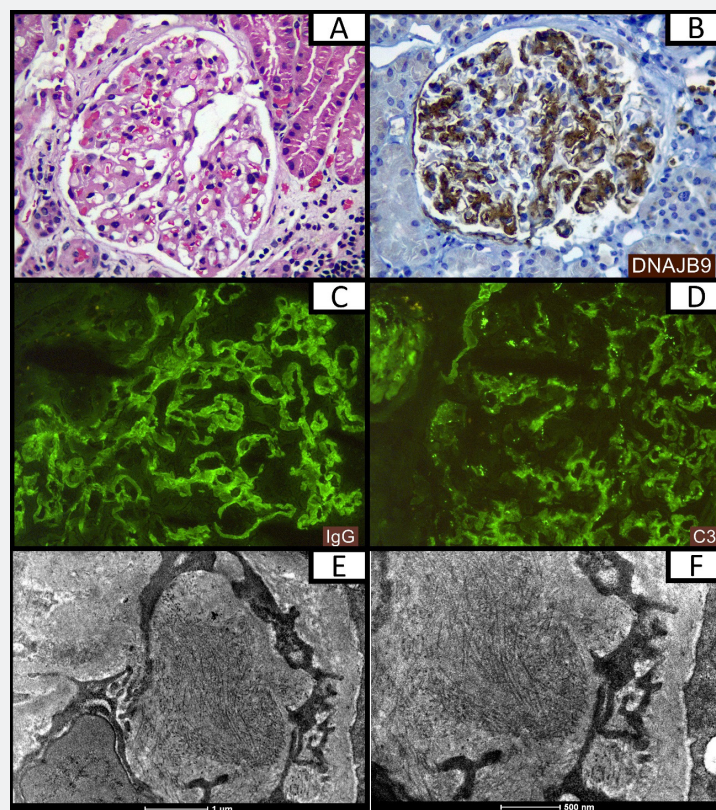
Until recently, the diagnosis of FGN was only possible performing light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM). The EM evidence accumulation of fibrils randomly oriented, straight and nonbranching, with measurements between 10 and 30 nm in thickness. The is prominent in mesangium and/or along the glomerular basement membranes [1,5,7,10]. IF, in most cases, shows smudgy glomerular staining for IgG, C3 and light chains (kappa and lambda). The IgG4 subtype is the most prevalent, presenting restriction in most cases (80%); moreover, light chains usually exhibit the same intensity of IF stain [1,5,6,11,12]. The LM can exhibit several morphological patterns, but in most cases it shows mesangial proliferation with or without duplication of the glomerular basement membranes (membranoproliferative glomerulonephritis), with crescentic lesions identified in approximately 25% of cases [1,5,6,7,13].

Congo red research is important to distinguish FGN from amyloidosis. Deposits in FGN are negative for Congo red, with no birefringence on the green apple under polarized light in the vast majority of cases. However, although infrequent, there is a study that shows Congo red positivity in some patients with FGN [14].

The evaluation of FGN is a diagnostic challenge in the practice of the pathologist, because the main diagnostic methods (LM, IF, ME) have limitations. There are no morphological characteristics with highly specific or pathognomonic lesion. Added to this is the fact that such characteristics can also be seen in several other glomerulopathies, such as: Amyloidosis, IgA Nephropathy, Diabetic Glomerulopathy, Immunotactoid Glomerulopathy, Fibronectin Glomerulopathy, Collagen-fibrotic Glomerulopathy, among other deposit glomerulopathies. In addition, access to EM is costly

and restricted to a minority of cases, especially in developing countries. Thus, it is clear that FGN is an underdiagnosed disease and that the use of a sensitive and specific biomarker can make an important contribution to renal pathology and the differential diagnosis of diseases with fibrillar deposits. In this context, a new proteomic biomarker, DNAJB9, has been discovered, which can be investigated by immunohistochemical technique and is useful for the diagnostic definition of FGN.

What is DNAJB9 and what is its importance in this context?



A - Glomerular mesangial expansion (hematoxylin and eosin, x400); B - Immunohistochemistry (DNAJB9) shows strong glomerular staining (x400); C - Immunofluorescence microscopy shows smudgy glomerular staining for IgG (x400). D - Immunofluorescence microscopy shows smudgy glomerular staining for C3 (x400). E and F - Electron micrographs exhibit fibrillar deposits composed of randomly oriented, straight, nonbranching fibrils.

Figure 1: Shows the morphological characteristics of a case of FGN by the techniques of LM, IF and EM.

DNAJB9 is a protein that contains 223-amino acids and is a member of the DNAJ family. DNAJ proteins participate of several fundamental roles, such as regulating ATPases activity, stressing the endoplasmic reticulum, inflammatory mediators actions, differentiating B lymphocytes and producing antibodies, in addition they have protective function against cell death and protects hematopoietic stems cells during stress [15-21]. In the mass spectrometry study, this protein deposition was identified

in the glomeruli of all patients diagnosed with FGN and this accumulation was not found in others glomerulopathies [4,22,23]. When deposited in the FGN, curiously, no structural protein change was identified [22]. The presence of DNAJB9 can be assessed by immunohistochemistry, which is available in some laboratories specialized in kidney pathology. The first studies with this marker have shown high sensitivity (98-100%) and specificity (99-100%) in the diagnosis of FGN [4,22,23].

Conclusion

The research of the DNAJB9 protein by immunohistochemical technique has shown high accuracy for the diagnosis of FGN, enabling the diagnostic differentiation with several other glomerulopathies, especially those that exhibit fibrillar deposits. Its discovery and applicability is promising and will allow greater diagnostic precision, avoiding errors and underdiagnosis of FGN.

Conflict of Interest

The authors declare that they have no conflict of interest

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