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REVIEW

Fibrillary Glomerulonephritis: An Update

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Fibrillary glomerulonephritis (FGN) is a rare proliferative form of glomerular disease characterized by randomly oriented fibrillar deposits with a mean diameter of 20 nm. By immunofluorescence (IF), the deposits stain for IgG, C3, and κ and λ light chains, suggesting that the fibrils may be composed of antigen-antibody immune complexes. A recent major advance in our understanding of the pathogenesis of FGN resulted from the discovery that a major component of the fibrils is DNA-J heat-shock protein family member B9 (DNAJB9), and immunohistochemical staining for DNAJB9 now makes it possible to diagnose FGN in the absence of ultrastructural evaluation. FGN has a poor prognosis, treatment options are currently limited, and transplant recurrence is not uncommon.

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FGN is a rare form of glomerulonephritis that was first described in 1977[1] and is defined by the ultrastructural finding of organized, randomly oriented, nonbranching fibrils with a mean diameter of 20 nm (range 15–25 nm). The diagnosis of FGN can only be established by renal biopsy, and the incidence of FGN in native renal biopsies is less than 1%.[2–5] The fibrils that characterize FGN are predominantly confined to glomeruli and stain intensely by IF for IgG, C3, κ, and λ, strongly suggesting that the fibrils are composed of a complex of antibodies and antigens. The absence of staining for Congo red (with rare exception) and the composition of the fibrils help to differentiate FGN from amyloidosis, while the diameter of the fibrils and the absence of a microtubular appearance with a hollow core help differentiate FGN from immunotactoid glomerulopathy.

Clinical Features

The 3 largest clinical series on FGN, which include a total of 187 patients, are reviewed in Table 1.[4–7] These clinical series include the initial series from Columbia University with 61 patients,[4] a cohort from the Mayo Clinic that initially included 66 patients[5] but was later expanded to include 84 patients,[6] and a more recent report of 42 patients from the University of North Carolina (UNC).[7] The clinical data from each of the 3 series are provided in Table 1, along with weighted averages of the 3 studies. The mean age of presentation was the sixth decade in all 3 cohorts, and 66% of patients were female. White race was most frequent, albeit less so in the UNC study, possibly related to demographics of the geographic region. At the time of presentation, 70% of patients had renal insufficiency, and the mean serum creatinine was 2.9 mg/dl. The mean 24-hour urine protein was 5.7 g/d, and 36% of patients met criteria for full nephrotic syndrome (defined by a 24-hour urine protein >3 g/d, serum albumin <3.5 mg/dl, and edema). Hematuria was documented in 82% of subjects.

The disease associations with FGN were somewhat more variable between the 3 studies. The prevalence of concurrent HCV infection ranged from 7% to 27% (mean, 13%); notably, all 7 of the patients with FGN and hepatitis C virus infection in the UNC series were African American. The prevalence of concurrent dysproteinemia, defined by the presence of a serum or urine M-spike or positive immunofixation, varied from 4% to 42% (mean, 13%). The clinical data were more consistent with respect to coexistent autoimmune disease, diabetes mellitus, and malignancy. Among patients with FGN, autoimmune disease was seen in 11% of patients, diabetes mellitus in 24%, and malignancy in 9%. Examples of autoimmune diseases seen in patients with FGN include Crohn's disease, lupus, Grave's disease, and idiopathic thrombocytopenic purpura. Given the incidence of these conditions, we recommend screening for hepatitis C virus, dysproteinemia, autoimmune disease,

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Table 1. Clinical characteristics of patients with FGN in the 3 largest cohorts

	Columbia (n = 61)	Mayo Clinic (n = 84)	UNC (n = 42)	Weighted average
Age, yr	57	59	54	57
White race, %	92	NA	71	83
Female, %	61	74	60	66
Creatinine, mg/dl	3.1	2.5	3.2	2.9
Renal insufficiency, %	69	71	NA	70
Proteinuria, g/d	6.4	5.1	5.7	5.7
Full nephrotic syndrome, %	52	25	NA	36
Hematuria, %	60	90	97	82
Hepatitis C, %	17 (6/34 patients)	7	27 (7/26 patients)	13
Autoimmune disease, %	5	14	13	11
Diabetes mellitus	20	24	28	24
Malignancy, %	7	10	12	9
Dysproteinemia, %	15 (7/46 patients)	4	42 (8/19 patients)	13

FGN, Fibrillary glomerulonephritis; UNC, University of North Carolina.

diabetes mellitus, and malignancy in patients with FGN.

Pathology

FGN is associated with 5 patterns of glomerular involvement by light microscopy, which correlate with clinical presentation and outcome[4] (Figure 1). The most common light microscopy appearance of FGN in the series from Columbia University was a membranoproliferative pattern (MPGN) in which there is mesangial proliferation and expansion, accompanied by glomerular basement membrane (GBM) duplication and cellular interposition that attenuate the capillary lumen[4] (Figure 1a and b). Glomerular capillary lumen attenuation and obliteration also are seen in the diffuse proliferative pattern of FGN, in which there is mesangial and *endocapillary* proliferation, often accompanied by infiltrating mononuclear leukocytes and crescent formation. In contrast, the mesangial proliferative pattern of FGN, which is the most common pattern in the majority of case series,[3,5,6] is characterized by solely mesangial proliferation and expansion in the absence of involvement of the glomerular capillary lumen. In the rare membranous pattern, there is GBM thickening with spike formation, which, similar to the mesangial proliferative pattern, is not accompanied by cellular proliferation or GBM duplication that attenuate capillary lumina. Lastly, the diffuse sclerosing pattern of FGN has been defined by the presence of >70% global glomerulosclerosis.[4] The mesangial proliferative and membranous patterns of FGN are associated with a lower serum creatinine level and a lower incidence of nephrotic syndrome at the time of presentation and the best long-term prognosis. Not surprisingly, the diffuse sclerosing pattern is associated with the worst prognosis, whereas the MPGN and diffuse proliferative patterns are intermediate with respect to presenting features and outcome. Notably, the most common pattern in the Columbia series[4] was MPGN (44% of biopsies), whereas the most common finding in the Mayo Clinic series[5] was the mesangial proliferative pattern, seen in 71% of patients, which may explain the better outcomes reported in the latter study. Of note, the fibrillary deposits are associated with mesangial and in some cases GBM expansion by weakly eosinophilic material that appears pale with the periodic acid–Schiff stain and blue-gray with the trichrome stain and are nonargyrophilic.

The IF findings in FGN include somewhat ill-defined, "smudged" deposits that stain most intensely for IgG (Figure 1c), usually accompanied by C3, κ, and λ, and sometimes also associated with staining for C1q, IgM, and/or IgA. In approximately 5% of cases of FGN, the deposits stain by IF for κ or λ, but not both.[4,6,7] This light chain restriction—a finding that suggests that the fibrillary deposits may have a monoclonal composition—often correlates with the presence of dysproteinemia. The deposits in FGN are nearly always present in a mesangial distribution, whereas GBM staining is present in most cases with the MPGN, diffuse proliferative, and membranous patterns. IF staining for subtypes of IgG most often reveals positivity for IgG1 and IgG4, in the absence of IgG2 and IgG3,[4] and the intensity of staining for IgG4 typically exceeds that for IgG1.[8] Of note, IF reveals focal positivity in tubular basement membranes in a significant minority of cases of FGN.

Ultrastructural evaluation is critical to establishing the diagnosis of FGN. Electron microscopy reveals nonbranching, randomly oriented fibrils with a mean diameter of 20 nm (range, 15–25 nm), which are nearly always present in the mesangial matrix and in most cases also permeate the lamina densa of the GBM, with minimal extension into the subendothelial or subepithelial regions (Figure 1d and e). Extensive foot process effacement is seen in areas of fibril accumulation. Intermixed electron-dense deposits of the usual, granular type are commonly

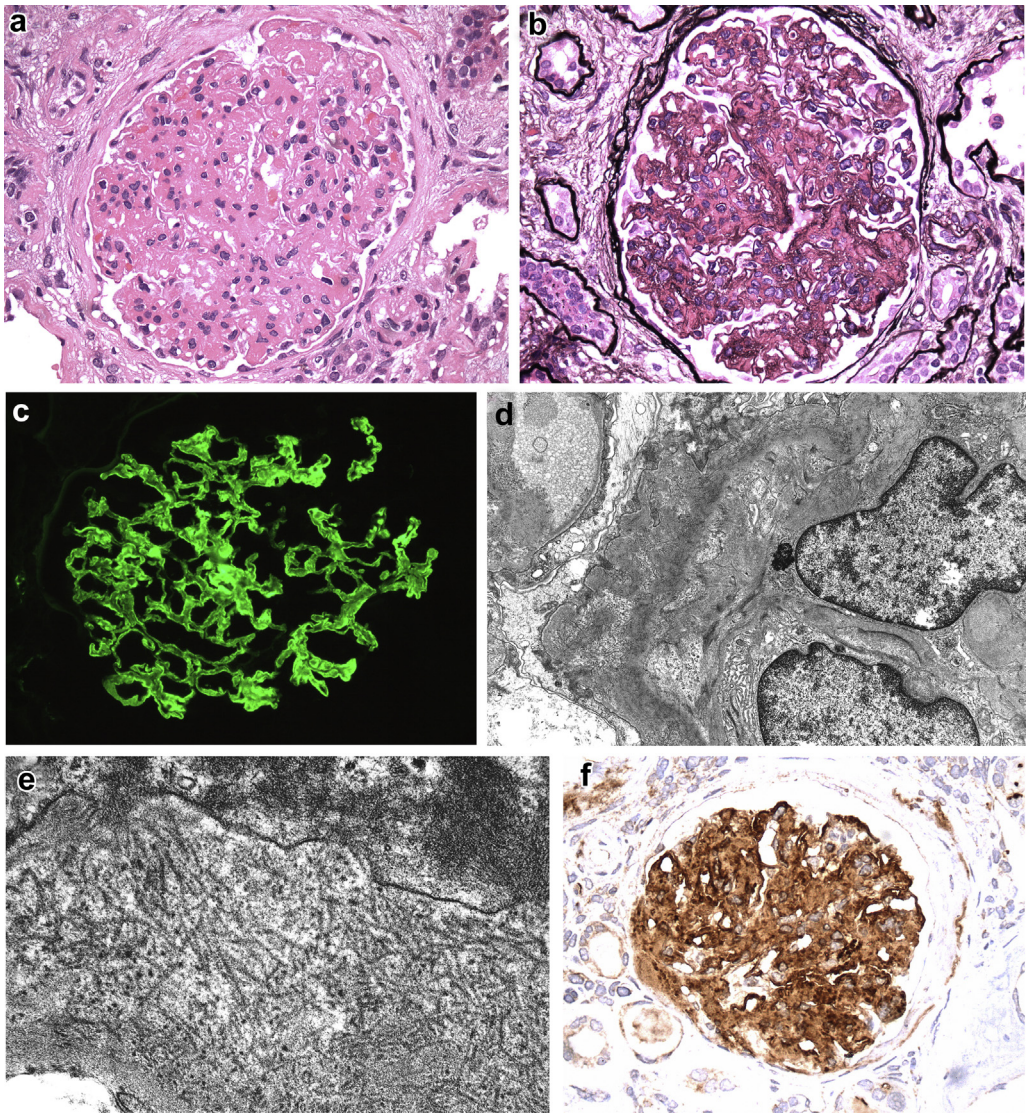

Figure 1. Renal biopsy findings in fibrillary glomerulonephritis (FGN). (a) A glomerulus exhibits global mesangial proliferation with expansion of the mesangial matrix by amorphous eosinophil material that corresponds with the fibrillary deposits and also involves and mildly expands the peripheral capillary walls of the glomerular basement membrane (GBM). In addition to mesangial proliferation, there is evidence of endocapillary proliferation with focal infiltrating mononuclear leukocytes (hematoxylin and eosin; original magnification ×400). (b) The Jones methenamine silver stain highlights the eosinophilic deposits that expand the mesangial matrix and GBMs, and also demonstrates segmental GBM duplication with cellular interposition ("membranoproliferative features"; original magnification ×400). (c) Immunofluorescence staining for IgG reveals intense global mesangial and glomerular capillary wall–ill-defined, smudged positivity. Identical staining for C3, κ, and λ was noted (original magnification ×400). (d) Ultrastructural evaluation demonstrates abundant fibrils that permeate and expand the GBM and also are seen in the mesangial matrix. Overlying visceral epithelial cells exhibit complete foot process effacement (original magnification ×12,000). (e) At higher magnification, the fibrils are randomly oriented with a mean diameter of 20 nm (original magnification ×60,000). (f) Immunohistochemical staining for DNA-J heat-shock protein family member B9 is strongly positive in the mesangial matrix and GBMs, which is the same distribution as the randomly oriented fibrils in this biopsy showing FGN (original magnification ×400).

encountered in FGN but typically are relatively focal in distribution. Of note, rare cases of cryoglobulinemic glomerulonephritis form fibrils with an ultrastructural appearance that is identical to FGN; as such, testing for circulating cryoglobulins is recommended before establishing a definitive diagnosis of FGN.

Pathogenesis

Until recently, understanding of the pathogenesis of FGN was limited, in part because of the lack of an available animal model for this condition. The observation that cryoglobulinemic glomerulonephritis can appear identical at the ultrastructural level to FGN, as well as the similar composition of the deposits by IF, raise the possibility of a similar pathogenesis. There is a single report of a patient with FGN for whom serum was stored at 4 °C for 4 months and then recovered.[9] The serum contained a cryoprecipitate that did not dissolve upon rewarming, suggesting that the fibrils of FGN might represent an irreversible "slow cryoglobulin."[9]

A major breakthrough in our understanding of FGN occurred in 2018 when 2 independent groups, working at the Mayo Clinic[10] and the University of Washington,[11] utilized laser capture microdissection to extract glomeruli from biopsy specimens of patients with FGN followed by liquid chromatography–assisted tandem mass spectrometry. These groups simultaneously identified DNAJB9 as one of the most abundant proteins in the FGN glomerular proteome, but it was not present in glomeruli with amyloidosis, other forms of glomerulonephritis, or normal controls. DNAJB9 was shown to co-localize with IgG and components of the classic complement pathway in glomeruli. These studies suggest that DNAJB9 may act as an autoantigen in FGN.

DNAJB9, also referred to as ERdj4 (or Mdg-1), is a 223-amino acid member of the DNAJ family of proteins that act as co-chaperones for the heat-shock protein 70 family members including, most notably, binding immunoglobulin protein.[12–15] The heat-shock protein 70 family members are thought to be important chaperones in the endoplasmic reticulum (ER), playing a role in protein folding, unfolding, translocation, and degradation. DNAJB9 functions as a co-chaperone to binding immunoglobulin protein, assisting in protein folding and the degradation of misfolded proteins, termed the "unfolded protein response." In particular, DNAJB9 may be important in the recognition of misfolded proteins in order to mark them for degradation[14] and also may inhibit the apoptotic effect of p53 on cells under conditions of cell stress,[15] leading to the suggestion that increased expression of DNAJB9 may represent a marker of increased ER stress.[14–16] DNAJB9 is present at low levels in the ER of most cell types. Nasr *et al.*[6] identified expression of DNAJB9 by immunohistochemical staining in the cytoplasm of neurons; gastrointestinal, pulmonary, gynecologic, and breast epithelium; and lymphocytes, to name a few. In the normal kidney, DNAJB9 is present at low levels in renal tubular epithelial cells, podocytes, and mesangial and endothelial cells. At present, the only disease known to be associated with large amounts of *extracellular* deposition of DNAJB9 is FGN.

With respect to the role of DNAJB9 in the development of FGN, peptide analysis has demonstrated that the DNAJB9 detected in FGN represents the full length, 223-amino acid protein, and genetic sequencing of 2 patients with FGN did not reveal pathogenic mutations.[10] The absence of additional components of ER stress pathways and unfolded protein response by mass spectrometry argue against a central role of ER stress in the pathogenesis of FGN.[11] These observations, as well as the co-localization of DNAJB9 with IgG and components of the classic complement pathway, suggest an autoimmune pathogenesis with DNAJB9 acting as the putative autoantigen. Many questions remain unanswered, including how DNAJB9 forms fibrils and whether this happens before or after binding to IgG. If FGN has an autoimmune pathogenesis, why haven't attempts to treat patients with immunosuppression been more successful? Of note, if overexpression of DNAJB9 plays a central role in the pathogenesis of FGN, then potential alternative pathways for treatment exist. DNAJB9 has been shown to be inducible by the Ras/Raf/extracellular signal–regulated kinase pathway in response to p53,[16] and several kinase inhibitors currently in use interfere with this pathway.[17] Additional steps in our understanding of FGN will include studies that examine circulating levels of DNAJB9 and anti-DNAJB9 antibodies, and the potential development of an animal model.

Data on the sensitivity and specificity of DNAJB9 staining for the diagnosis of FGN are convincing. In the largest study to date that includes renal biopsy specimens from patients with FGN (84), amyloidosis (21), other forms of glomerular disease (98), and healthy normal control subjects (11), staining for DNAJB9 was found to have a sensitivity of 98% and specificity of 99% for the diagnosis of FGN[6] (Figure 1f). Of note, the 2 cases of FGN that lacked staining for DNAJB9 were atypical in that the IF staining was positive for IgG but negative for both κ and λ. The single non-FGN case with positive staining for DNAJB9 exhibited findings most compatible with smoking-associated nodular glomerulosclerosis and exhibited only focal staining in 2 of 17 glomeruli, rather than the diffuse staining typical of FGN. Thus the reported sensitivity of 98% and specificity of 99% may represent an underestimate. Of note, all 9 biopsies with immunotactoid glomerulopathy and 6 with cryoglobulinemic glomerulonephritis were negative, supporting the distinction between FGN and these entities.[4] Importantly, the availability of immunohistochemical staining for DNAJB9 as a marker of FGN allows for more rapid diagnosis of this entity and, more importantly, provides a method to establish the diagnosis of FGN in the many areas of the world in which electron microscopy is not readily available.

A recent report from the Mayo Clinic illustrates how the discovery of DNAJB9 in FGN can have practical implications.[18] The report described 18 patients with renal biopsy findings compatible with FGN, but the deposits exhibited apple-green birefringence when stained with Congo red and viewed under polarized light.[18] This demonstration of "Congophilia" is a characteristic feature of amyloidosis that often is used to exclude the diagnosis of FGN. Mass spectrometry and

immunohistochemical staining revealed abundant expression of DNAJB9 and the absence of a proteomic signature of amyloidosis. As such, these cases were appropriately labeled "Congophilic fibrillary glomerulonephritis," a diagnosis that previously could not have been made and that could have led to the inaccurate diagnosis of amyloidosis, with significant treatment implications.

Treatment and Prognosis

The prognosis for patients with FGN remains poor, with limited data to suggest optimal therapy. In the series from Columbia University, the median time to end-stage renal disease (ESRD) was 24.4 ± 15.2 months, and predictors of outcome on multivariate analysis included initial serum creatinine and degree of interstitial fibrosis.[4] In the initial series from the Mayo Clinic, 44% of patients reached ESRD during a mean follow-up period of 52.3 months, and the strongest predictor of outcome on multivariate analysis was initial serum creatinine, followed by age, 24-hour urine protein, and degree of glomerulosclerosis.[5] On univariate analysis in both studies, the pattern of glomerular involvement seen by light microscopy affected clinical outcomes, and the increased presence of a mesangial pattern in the Mayo Clinic cohort likely played a role in the better prognosis reported in that series. In the series from UNC, the median time to ESRD was 13 months, with poorer outcomes in African American patients.[7]

Immunosuppressive treatment was administered to 36% of patients in the series from Columbia University and 48% of patients in the series from the Mayo Clinic and UNC.[4,5,7] The most common form of treatment was steroids, with or without a second agent, including most notably cyclophosphamide or rituximab. A benefit of immunosuppression could not be detected in these small, retrospective studies in which patients with more severe disease were more likely to have been treated. In 2013, Javaugue *et al.*[8] reported that 5 of 7 patients with FGN who were treated with rituximab (2–4 injections of 375 mg/m^2) attained a partial remission, defined by a >50% decrease in 24-hour urine protein accompanied by <15% decline in estimated glomerular filtration rate, compared with baseline. In this series, only 1 of 3 patients treated with cyclophosphamide, 0 of 5 patients treated with steroid monotherapy, and 0 of 4 patients treated with cyclosporine had a response. Of note, baseline estimated glomerular filtration rate was higher in responding patients (76 vs. 42 ml/min).

In 2014, Hogan *et al.*[19] published a report on the largest series of patients with FGN who were treated with rituximab. This series included 12 patients, the majority of whom had an MPGN pattern revealed by light microscopy. The serum creatinine level at baseline ranged from 0.7 to 3.0 mg/dl, with a serum creatinine level >1.2 mg/dl noted in 9 of 12 patients. The majority of patients had not received prior immunosuppression, and most (11 of 12) received 2 doses of rituximab separated by 2 weeks. Four of the 12 patients (33%) had appeared to have a clinical response, referred to as "nonprogression" and defined by stable renal function, over a follow-up period of 14 to 83 months (mean 40 months); 3 of the 4 patients also had a significant decline in proteinuria. However, the remaining 8 patients experienced progressive renal disease, including 5 who reached ESRD. Of note, the "nonprogression" group included all 3 patients with a baseline serum creatinine ≤1.2 mg/dl. In the UNC series, only 1 of 9 patients treated with rituximab met criteria for "nonprogression."[7] Conclusions regarding immunosuppressive therapy for FGN cannot be drawn from these limited data, although rituximab may offer benefit in patients with FGN, particularly in patients with relatively normal baseline renal function. Additional studies are needed to address this issue.

Transplantation

Fourteen patients with ESRD secondary to FGN at the Mayo Clinic underwent renal transplantation, including 5 with preemptive transplants. At a mean follow-up of 51 months, 5 patients (36%) had a biopsy-proven recurrence of FGN, including 2 patients who lost their allograft as a result of FGN recurrence.[5] Two patients in the Columbia series underwent renal transplantation; neither had a clinical recurrence at 4 and 8 years of follow-up, although neither patient had undergone a renal allograft biopsy.[4] A recent report from Australia and Zealand, using the ANZDATA registry, reported on the outcomes of 13 patients who had ESRD resulting from FGN and received allografts.[20] Only 1 of the 13 patients had a recurrence of FGN, which ultimately led to allograft failure 4.6 years after the recurrence was diagnosed. Outcomes for transplantation in FGN were similar to the overall transplant population with respect to 10-year patient and renal allograft survival.[20] In summary, renal transplantation is a viable option for patients with FGN, but the risk of recurrence is not negligible.

In conclusion, FGN is a rare form of glomerular disease characterized by distinctive randomly oriented, nonbranching fibrils with a mean diameter of 20 nm (range 15–25 nm). Recent studies indicate that the fibrils contain IgG, complement components, and DNAJB9, the latter of which now makes it possible to diagnose FGN in the absence of electron microscopy. The prognosis for FGN is poor, therapeutic options

are limited, and optimal therapy remains to be defined.

DISCLOSURE

All the authors declared no competing interests.

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