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Fibrillary and Immunotactoid Glomerulonephritis

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Abstract

Renal diseases involving glomerular deposits of fibrillary material are an important diagnostic challenge for the ultrastructural pathologist. Two primary disorders of this type, termed ``fibrillary glomerulonephritis'' (characterized by fibrils measuring approximately 20 nm in diameter) and ``immunotactoid glomerulopathy'' (characterized by larger, microtubular deposits), have been described. The possible relatedness of these two disorders and their potential association with other systemic illnesses are subjects of current debate. Other multisystemic diseases, including amyloidosis and various forms of cryoglobulinemia, can also present with fibrillary or microtubular deposits in the kidney.

The distinction between fibrillary glomerulonephritis, immunotactoid glomerulopathy, and other processes that have similar ultrastructural features are discussed in the present review.

Keywords: *fibrillary glomerulonephritis; immunotactoid glomerulonephritis; cryoglobulinemua; amyloidosis; fibrillary deposition; microtubular deposition*

Introduction

Fibrillary glomerulonephritis (FGN) and immuno tactoid glomerulonephritis (ITG) are common renal diseases characterized by fibrillary amyloid-like glomerular deposits. FGN was first described in 1977 and is characterized by straight fibrils of 10-30 nm thickness with polyclonal immunoglobulin deposition (1).

Research Methodology

Because aim of this review is to find out what is really new in the classification and differentiation between fibrillary and immunotactoid glomerulonephritis, we have analyzed the available papers on fibrillary and immunotactoid glomerulonephritis, by a review of the currently available papers. A literature search was performed using PubMed (NCBI/NIH) with the search words "fibrillary glomerulonephritis", "immunotactoid glomerulonephritis". As first line research the papers published in the last three years were examined. Paper selection has been made according the relevance of the journal, the authors, the dimension of the study and the novelty of the findings. So doing 20 papers recently published have been selected, then we proceeded in a backward way and studies previously published have also been included.

Epidemiology and Distinction between Fibrillary Glomerulonephritis and Immunotactoid Glomerulonephritis

FGN has been reported to account for 0.5-1.0% of glomerulonephritis, ITG is tenfold rarer (2) and has been reported initially in 1992 (3). Several authors suggest that fibrillary and microtubular Ig deposits should be considered as variants of the same glomerulopathy referring the disease to a fibrillary immunotactoid glomerulonephritis (4, 5). Other authors claim that is essential to distinguish between immunotactoid (microtubular) GN and fibrillary GN (6, 7).

Both diseases are most commonly idiopathic, but ITG in particular, may be associated with monoclonal gammopathies (8), chronic infections (9, 10).

In ITG, in addition to monoclonal gammopathy, hematological malignancy may be associated (11).

To date the majority of the authors retain that FGN should be kept distinguished from ITG on immunopathologic, ultrastructural and clinical grounds (6, 11, 12, 13). Table 1 reports the main immunologic and clinical characteristics that distinguish fibrillary and immunotactoid glomerulonephritis.

Table I Immunologic and Clinical Characteristics of Fibrillary and Immunotactoid Glomerulopathies

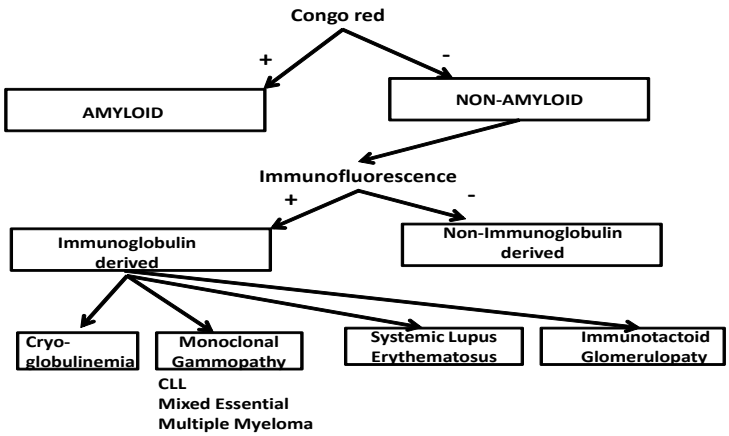
Characteristics	Amyloidosis (AL Type)	Fibrillary Glomerulopathy	Immunotactoid Glomerulopathy
Congo red staining	Yes	No	No
Composition Fibrils or microtubules size Organization in tissues	Fibrils 8-15 nm Random	Fibrils 12-22 nm Random	Microtubules ➢30 nm Paralloel arrays
Immunoglobulin deposition	Monoclonal LC	Usually polyclonal (mostly IgG4)	Usually monoclonal
Glomerular lesions	Deposits spreading from mesangium	MPGN, CGN, MP	Atypical MN, MPGN
Renal presentation Extrarenal manifestations Association with LPD	Severe NS, Absence of hypertension Systemic deposition disease Yes (myeloma)	NS with hematuria, RPGN Pulmonary hemorrahge Uncommon	NS with hematuria and hypertension Microtubular inclusions in leukemic lymphocytes Common (CLL, NHL, MGUS)
Treatment	Melphalan + dexamethasone	Corticosteroid + Cyclophosphamide	Treatment of the associated LPD

CGN, crescentic glomerulonephritis; CLL, chronic lymphocytic leukemia; GN, glomerulonephritis; LC, light chain; LPD, lymphoproliferative disorder; MGUS, monoclonal gammopathy of undetermined significance; MN, membranous nephropathy; MP, mesangial proliferation; MPGN, membranoproliferative glomerulonephritis; NHL non-Hodgkin lymphoma; NS, nephritic syndrome; RPGN, rapidly progressive glomerulonephritis

Indeed, ITG, which is 10-fold rarer that FGN is characterized by glomerular deposition of larger microtubular structures (usually > 30 nm in diameter) that have focal parallel alignment.

In contrast to FGN, patients with ITG frequently have hypocomplementemia and an underlying dysprotidemia. The glomerular deposits are usually monoclonal (14). The distinction between the two forms is not always easy and a useful algorithm is that shown on figure 1 (15).

Figure 1 FIBRILLARY GLOMERULOPATHIES



In a study by Fogo et al (16) which reviewed their patients, was found that patients affected by FGN were significantly younger than patients with ITG.

All patients were affected by marked proteinuria and microscopic hematuria. 70% of patients with ITG had an associated hematopoietic disease with monoclonal proteins and abnormal plasma cell proliferation. In GFN the microfibrils had a diameter of 14 +/- 0.5 nm, while the microtubular structures had a mean diameter of 42.3+/-0.3 nm.

More recently, Fogo et al (17, 18) identified as key diagnostic features for FGN: 1)Mesangial proliferation and variable endocapillary proliferation; 2)Polyclonal immunoglobulin G and C3; 3)Randomly arranged fibrils in the mesangium and variably in the glomerular basement membrane (GBM), 12-22 nm in diameter and negative for Congo red stain. Similarly, key diagnostic features for ITG were 1) Mesangial proliferation and variable endocapillary proliferation; 2) Often clonal Ig and light chain restriction; 3)microtubular in parallel array in the mesangium and variably in GBM, > 30 nm in diameter.

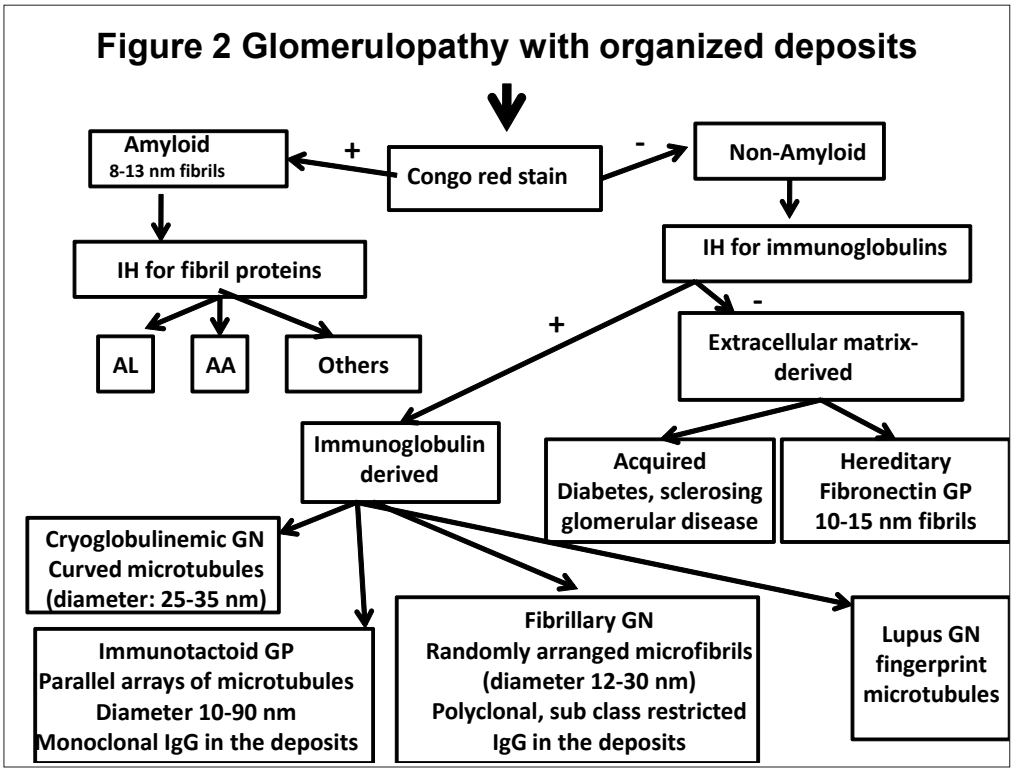
The distinction between the two entities is not always easy because many diseases affecting the kidney may present similar structures in the kidney. This point is well highlighted by a study reporting five cases of patients that presented in the kidney biopsies fibrillary deposition (19). The authors stress that the comprehensive analysis of fibrillary glomerulopathies should include a perfect assessment of ultrastructural features (fibril diameter and substructure), exclusion of amyloidosis, correlation between light microscopy, histochemistry and immunofluorescence and a careful search for underlying conditions such as lymphoma, chronic disease and cryoglobulinemia.

Fibrillary Glomerulonephritis

Fibrillary GN was first reported in 1977 (1) as a glomerulopathy with material very similar to amyloid that did not stain with Congo Red, even if recently, a variant has been identified that is Congo Red positive (20). The term was later changed by Duffy (21) that introduced the term of "fibrillary renal deposits and nephritis". Finally, Alpers (22) shortened the name to FGN.

FGN is characterized by the deposition of randomly arranged microfibrils with a diameter from 12 to n30 nm. At immunofluorescence polyclonal IgG and C3 are present. In light microscopy several histological patterns may be observed ranging from membranoproliferative GN, to mesangial proliferative GN, to diffuse proliferative GN or membranous thickening of the capillary tuft (23).

Figure 2 Glomerulopathy with organized deposits



For the diagnosis, the use of electron microscopy is mandatory.

Clinically, FGN is manifested by proteinuria, often in the nephrotic range. The disease course is generally progressive towards end stage renal disease (ESRD). Fibrils recur in 50% of the transplanted kidneys, but the recurrence is often benign (24).

The pathogenesis of fibrillogenesis has not yet been elucidated. Fibril depositions are in general renal limited, even if some reports refer extrarenal involvement (25). According other authors, these reports should be interpreted with caution (26). In a series reported of FGN, fibrils co localize with amyloid P (27). In other series fibronectin has been detected in the deposits (28), but it appears that fibronectin is not an essential component of the fibrils. All these findings allowed to improve the diagnostic algorithm shown in figure 1 (figure 2)

AL, amyloid light chain; AA, amyloid associated protein; IH, immunohistochemistry; GN, glomerulonephritis; GP, glomerulopathy

In a recent study (29) a DnaJ omolog subfamily member 9 (DNAJB9) has been detected in patients affected by FGN. The proteome of these patients also contained IgG1 as the dominant Ig. In these patients immunofluorescence and immunohistochemistry with an anti-DNAJB9 antibody showed a strong and specific staining of the glomeruli similar to immune-deposits. These findings confirmed a previous study (30) and allow to identify DNAJB9 as a putative autoantigen in fibrillary GN. Recently was developed an immunoprecipitation-based multiple reaction that allowed to measure serum levels of DNAJB9. In patients affected by FGN a 4-fold higher abundance of serum DNAJB9 was found and this suggested that serum levels of DNAJB9 could be a valuable marker to predict FGN (31).

A different study (20) found that the proteomic signature of amyloid was not detected using mass spectrometry among cases of congophilic fibrillary GN. Additionally, DNAJB9 was not detected using mass spectrometry in all cases of FGN regardless of congophilia and was absent in cases of amyloidosis and in healthy individuals.

In conclusion, the distinction between FGN and should not be done only on congophilic properties, but identifying the presence of DNAJB9 with mass spectrometry and immunohistochemistry.

The prognosis of FGN is poor, although remission may occur in a minority of patients without immuno suppressive therapy (32).

The published experience on the treatment of FGN includes several cases reports using the blockade of angiotensin II and a variety of immunosuppressive treatment including steroids and other immuno suppressants (14). However, no treatment has been shown to improve the long-term outcomes.

Recently, a study used rituximab therapy (33) that docomented its efficacy principally in patients non-progressor and with ban early diagnosis.

Immunotactoid Glomerulonephritis

Immunotactoid glomerulopathy (ITG) was first described by Schwartz and Lewis (11) to describe a glomerular disease characterized by the presence of Congo-red negative organized deposits that stain for IgG and complement. It is also defined by the glomerular deposition of microtubules that have distinct hollow centers, which can range in size from 10 to 90 nm (34). Because the deposition in ITG can appear similar to those in cryoglobulinemia and lupus nephritis, these entities must be ruled out before a diagnosis of ITG can be made. Since the first descriptions, the majority of published series included patients with underlying hematologic malignancies, excluding patients with systemic lupus erithematosus or cryoglobulinemia (11, 12, 16).

In the study of Rosenstock (12), the incidence of serum or urine monoclonal gammopathy was 67% in patients with ITG versus 15% in those with FGN. Comparatively, patients with ITG have a significantly higher rate of paraproteinemia than those with FGN (33 % vs 7%) (5).

The disease is very rare and the pathogenetic mechanism of fibrils deposition is not completely understood. The deposition should account for three features: the Ig found in the deposits must be produced by lymphocytes and / or plasma cells; the Ig precursors must reach the kidney via the circulation; the exclusive glomerular localization of the deposits implies a role for local factors in fibrillogenesis.

Recent studies on CD2 associated proteins (CDap) in knockout mice provide the support for a defect in glomerular function in ITG that could be responsible for tactoid formation and suggest that the effect is localized to the podocyte (35, 36).

Patients present with nephritic proteinuria, reduced glomerular filtration rate and hypocomplementemia.

Histologically the disease may present as a membranoproliferative GN, a diffuse proliferative GN or a membranous glomerulopathy. The disease may recur after transplantation. The electron microscope shows microtubular, often parallel arrays with a diameter > 30 nm.

The key diagnostic features are a mesagial proliferation with clonal IgG and light chain restriction on the already described microtubules.

Ig is significantly more frequently associated with monoclonal protein and hematopoietic malignancy, most often B cell related.

The clinical improvement of proteinuria when treatment was directed at the hematopoietic disorder, further support a role for monoclonal proteins in these patients.

Treatment with steroids alone or combined with cyclophosphamide, chlorambucil or melphalan has been successfully used to induce complete or partial remission of the nephritic syndrome: Fludarabin (2) or a combination of high-dose methylprednisolone and rituximab followed by alemtuzumab (37) has been shown to reduce proteinuria and improve renal function.

With a better understanding of the pathogenesis, clone directed strategies, such as rituximab against CD20 expressing B cells and bortezomib against plasma cell clones, have recently been used in the treatment of this disease (38).

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