Editorial

Should All Patients with Nephrotic Syndrome Undergo a Renal Biopsy?

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Nephrotic syndrome (NS) is defined by proteinuria exceeding 3.5 g per 24 hours, hypoalbuminemia, hyperlipidemia, and peripheral edema. Rather than being a distinct disease, NS is a clinical manifestation of underlying renal disease.[1] NS has the potential to cause serious complications, both related to the disease itself and due to the therapy given. Therefore, the NS diagnosis must be accurate to provide more targeted therapy decisions.

In the diagnostic process, renal biopsy serves as an essential component. Standard evaluation of biopsy specimens consists of light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). At the same time, standard staining includes hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), Masson's trichrome, Jones-methenamine silver, and Congo red staining if amyloidosis is suspected. However, these standard examinations are still challenging to provide optimally in many centers. Fortunately, recent advancements, particularly in the evolution of new antibodies (e.g., PLA2R-ab and Nephrin-Ab), have introduced new opportunities for non-invasive NS diagnostics with promising potential for current and future applications.

The following presents some of the causes of NS and the extent to which a renal biopsy is needed to confirm the underlying disease.

- **Minimal Change Disease (MCD).** MCD accounts for about 10% of NS cases in adults and is primarily idiopathic. The pathological features of MCD are loss of foot processes on EM but normal on LM and no complement or immunoglobulin (Ig) deposits on IF. It is suspected that a systemic process causes the production of glomerular permeability factors, such as autoantibodies, to nephrin. However, MCD has also been linked to secondary factors, including malignancies, infections, and drug use.[1,2]
- **Diagnosis**. Renal biopsy is necessary for diagnosing MCD in adults, as no specific laboratory test is capable of distinguishing MCD from other forms of NS. Following the diagnosis of MCD, the next step is to assess potential secondary causes.[2]

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- **Focal Segmental Glomerulosclerosis (FSGS).** FSGS is a pattern of kidney damage primarily affecting podocytes, which in LM is indicated by sclerosis observed in parts (segmental) of some glomeruli (focal). Depending on the underlying cause, FSGS can be classified into primary, secondary, and genetic forms.[1] The pathogenesis of primary FSGS likely involves circulating factors that cause podocyte dysfunction, typically leading to effacement of the foot processes.
- **Diagnosis.** Renal biopsy is essential for identifying FSGS lesions. Since FSGS represents a histologic pattern rather than a distinct disease, detecting these lesions should prompt an evaluation of the underlying cause. Differentiating primary from secondary FSGS requires assessing the absence or presence of NS, the degree of podocyte foot process effacement (usually diffuse in primary FSGS and segmental in secondary FSGS), and risk factors associated with secondary FSGS. However, these clinical and pathologic characteristics do not suffice for identifying a genetic cause of FSGS. Consequently, genetic testing is advisable in patients whose diagnosis remains unclear after clinicpathologic assessment.[1]

- **IgA nephropathy (IgAN).** IgAN is the most prevalent form of primary glomerulonephritis worldwide but rarely presents with NS. Renal biopsies in some IgAN patients with NS showed inconsistent findings, including mesangial IgA deposition and mild histologic lesions. However, EM showed extensive effacement of the foot processes, similar to that observed in MCD, thus defining it as MCD-IgAN.[3]
- **Diagnosis.** The diagnosis of IgAN can only be confirmed through renal biopsy, with the detection of IgA deposits on IF. This is because, to date, no specific laboratory findings are available to diagnose IgAN. However, renal biopsy also depends on the clinical presentation, which may not be necessary for every patient suspected of having IgAN. In cases of isolated hematuria without proteinuria and impaired renal function, biopsy is typically not performed, as it would not change therapy. However, indications for renal biopsy vary geographically.[1]

- **Lupus Nephritis (LN).** Membranous LN (class V LN) occurs in more than 20% of patients with LN and may coexist with class III or IV LN.[4] There are two mechanisms underlying membranous LN. First, through the formation of auto-antibodies against nuclear antigens and antibodies against C1q, Sm, Ro, chromatin, ribosomes, and others;[1] cationic antigens can penetrate the anionic glomerular base-ment membrane (GBM) and deposit in the subepithelial space, leading to antibody binding and in situ immune complex formation. Second, through the formation of circulating antibodies against podocyte-specific antigens, such as the exostosin 1/ exostosin 2 (EXT1/2) complex and neural cell adhesion molecule 1 (NCAM).[5,6] Both mechanisms can activate local complement; however, the GBM separates chemoattractants from the blood, and immune cell recruitment is minimal. Therefore, injury is confined to podocytes, leading to proteinuria without renal dysfunction in most cases.[1]
- **Diagnosis:** Standard diagnosis requires biopsy. Pure class V LN is characterized by thickening the glomerular capillary wall in LM and subepithelial immune deposits similar to MN in EM. However, typical of class V LN not found in MN are IgA, IgM, IgG, C3, and C1q along more than half of the glomerular capillary loop in IF.[1]

- **Membranoproliferative glomerulonephritis (MPGN).** Subendothelial immune complex deposits characterize MPGN and typically manifest as a combination of nephrotic/nephritic

syndrome and decreased complement C3.[7] The hallmarks of glomerular injury on renal biopsy include (a) thickening or double contour of the GBM on silver staining and (b) endo-capillary and mesangial hypercellularity.[1]

- **Diagnosis.** Renal biopsy is crucial for diagnosing MPGN. The classification falls into immune complex-mediated MPGN (I-MPGN), complement-mediated MPGN (C-MPGN), and without Ig or complement deposition[8] based on IF microscopy findings. C-MPGN is now referred to as C3 glomerulopathy (C3G), which includes two major subtypes—C3 glomerulonephritis (C3GN) and dense deposit disease (DDD)—according to the different patterns of C3 deposition in EM.[9]

- **Membranous nephropathy (MN**). MN is the leading cause of primary NS in adults. The characteristic injury pattern on renal biopsy includes thickening of the GBM and subepithelial Ig deposits with or without minimal cellular proliferation or infiltration. Clinical signs of NS develop slowly as the accumulation of immune complex deposits occurs gradually, often making it challenging to identify its onset. Proteinuria in MN can vary, ranging from subnephrotic to severely nephrotic. Renal function is generally preserved; most patients maintain normal blood pressure.[1]
- **Diagnosis.** Currently, MN is the only possible cause of NS immune-mediated based without renal biopsy. Although many autoantibodies have been identified for diagnosing MN[1], to date, only PLA2R-ab has been shown to help diagnose primary MN. Renal biopsy is unnecessary if anti-PLA2R-ab serology is positive, there is no indication of secondary causes, and renal function remains normal.[10] A biopsy is only indicated if anti-PLA2R-ab is negative, there is impaired renal function, and there is evidence of secondary causes. If the findings are consistent with MN, the biopsy specimen should also be examined for PLA2R staining. Anti-PLA2R-ab levels can also monitor response to therapy.[10] If anti-PLAR2 titers are undetectable, immunosuppressive therapy can be discontinued, and if increasing titers are found, therapy modification is necessary.[1]

Based on the brief description above, it can be concluded that every patient with NS should always undergo a kidney biopsy and standard microscopic examination and staining. Only NS due to MN can be diagnosed without renal biopsy, with positive anti-PLA2R antibodies, provided that renal function is normal and there is no evidence of secondary causes. However, the current evidence is still limited to patients with positive anti-PLA2R antibodies and is unclear for patients with positive THSD7A.

Declarations

Competing interest

The author declares no conflict of interest.

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