

Original article

Title: Renal biopsies after 70 years of age: a retrospective longitudinal study from 2000 to 2007 on 150 patients in western France.

Authors : Emilie Pinçon, MD¹, Nathalie Rioux-Leclercq, MD, PhD^{2,3}, Thierry Frouget, MD¹, Patrick Le Pogamp, MD¹, Cécile Vigneau, MD, PhD^{1,3}

Affiliations : ¹Nephrology Department, CHU Pontchaillou, Rennes, France ²Pathology Department, CHU Pontchaillou, Rennes, France ³UMR 6061/ IFR 140, Rennes 1 University, Rennes, France

Corresponding author: Pr Cécile Vigneau: Service de néphrologie, CHU Pontchaillou, 2 rue H Le Guilloux, 35033 Rennes Cedex ; tel 02 99 28 43 96 ; fax : 02 99 28 41 50 ; email : cecile.vigneau@chu-rennes.fr

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Abstract

Background: The elderly are more often referred to nephrologists and questions about indications for renal biopsy are increasing. The vascular lesions that appear with aging make the diagnosis of additional nephropathy more difficult. The purpose of our study is to investigate the characteristics of renal biopsies in the elderly in order to evaluate the indications and their use in guiding specific therapeutic interventions.

Methods: Patients over 70 years who underwent a renal biopsy between 2000 and 2007 in Rennes University Hospital were retrospectively analysed for biopsy complications, clinical features, diagnosis, therapy and its complications, evolution and mortality.

Results: Among the 150 renal-biopsied patients, 60% had a glomerulopathy and 30% had nephrotic syndrome. Biopsy complications occurred in 3.3%. 64% of nephrotic patients received immunosuppressive treatment and 62% of them developed drug-associated complications. In the treated group, there was more remission and survival at day 1000 was improved.

Conclusions: Renal biopsy may be indicated in the elderly, because it often gives a therapeutically useful diagnosis and complications are rare if contra-indications are respected. Kidney biopsy revealed histological diagnoses that were not usually suspected by the clinical presentation. In addition, immunosuppressive therapy did not alter the mortality rate, but did increase survival at 3 years.

Keywords: Elderly, prognosis, renal biopsy, therapeutics

Conflict of interest: none

1. Introduction

Since vascular lesions often develop in the kidney with age, and complicate the often present glomerulosclerosis of aging ¹, the clinical diagnosis of glomerulopathy might be more difficult in the elderly and require histological assessment of renal structure. In this retrospective study, we investigated specific characteristics of aging patients undergoing renal biopsy, particularly those with the nephrotic syndrome, in order to evaluate the indications for renal biopsy and evaluate current treatments in the population of elderly patients.

The indications for renal biopsy in the elderly are increasing. In Japan, a recent study showed that 15.1% of patients undergoing a renal biopsy in 2005 were more than 65 year old, compared to 8.2% in 1995 ². In Italy, one centre reported that 38% of the biopsied patients are now more than 65 year old ³ and in United Kingdom, 12% of kidney biopsies were done in patients over the age of 60 in 1978 to 30% in 1990 ¹. In western France, a unique study reported that mean age for renal biopsy in 1976 was 35 years and 52 years in 2000 ⁴. These modifications could be explained in part by the increase in longevity, but also by the improvements of physiological health status in aging. Thus, the indications to kidney biopsy and/or specific treatments in elderly may need to be re-evaluated.

Why might renal biopsy be informative in aging patients? First, the clinical presentation is often confusing in the elderly because of multiple associated conditions. For instance, the clinical presentation of acute renal disease, requiring specific treatment, may be

unusual superimposed on a chronic vascular or diabetic nephropathy⁵. Secondly, kidney biopsy may be more risky than at a younger age, due to cortical atrophy, and the co administration of anticoagulant or anti-platelet therapy due to cardiovascular disease. However, a few studies have shown that the incidence of complications in the elderly is not greater than that in younger patients⁶⁻⁸. Finally, specific treatment for glomerulopathy is often based on corticotherapy and/or immunosuppressive drugs which have serious side effects. Thus, giving them to an elderly patient without a biopsy-proven diagnosis may not be acceptable. On the other hand, not giving the appropriate therapy to “physiologically-young elderly” who would benefit would also be unacceptable^{2, 6, 9-11}.

In any event, consideration for performing a kidney biopsy must include careful checking for contra-indications: small kidneys, anticoagulant or antiplatelet therapy, bleeding disorders, uncontrolled hypertension or inability to remain recumbent for a few hours.

The objective of this study was to determine if our kidney biopsy policy in nephrotic elderly patients led to a diagnosis without an unacceptable complication rate. And that this diagnosis led to a specific treatments permitting improvements in renal function and patient survival. Our policy for renal biopsies in aged patients includes the following indications: proteinuria with extra-renal signs suggestive of systemic disease; nephrotic syndrome in absence of long history of diabetes or established amyloidosis; acute renal failure without evident explanation or rapid regression, unexplained chronic renal failure. However, to our mind, renal biopsy is not indicated in elderly patients with well- documented, slowly progressive renal insufficiency.

For this purpose, we retrospectively analyzed all the kidney biopsies done in patients over the age of 70 years, with a focus on treatment and prognosis of those presenting with nephrotic syndrome. We chose this focus since most of the articles in the literature examined the indications and results of renal biopsy ^{2, 3, 9, 12-14 15}, but very few examined the follow-up after specific treatments.

2. Materials and methods

2.1 Methods

Using the logiciel Cristal-Report© from the pathology department, the list of all patients, aged over 70 years, who had undergone one or more renal biopsy between the 01/01/2000 and the 12/31/2007 was established. Renal transplant and biopsies for neoplasia were excluded.

The logiciel “portfolio” from Pontchaillou hospital has been reviewed for clinical data: age, indication and date of renal biopsy, presence or absence of nephrotic syndrome and final diagnosis. The entire file of all the nephrotic patients was searched for:

- sex, age, weight
- treatment and previous diseases
- number of renal biopsies, complications of renal biopsies
- proteinuria (g/24h), total serum protein (g/l), albumin (g/l), creatinine $\mu\text{mol/L}$, and renal function (calculated by the simplified MDRD formula (Modification of Diet in Renal Disease ¹⁶) at the time of renal biopsy
- hematuria, presence of edema, hypertension
- hypercholesterolemia (yes or no)
- treatment: immunosuppressive treatment, treatment by ACEi (Angiotensin Converting Enzyme inhibitor) or ARB (Angiotensin II Receptor Blocker), anticoagulation or antiplatelet therapy, other treatments
- remission or persistence of nephrotic syndrome

- treatment complications
- thrombotic complications
- evolution of renal function
- date of death.

Kidney biopsies were done by an urologist or a nephrologist under ultrasound guidance.

2.2 Pathology studies

All renal biopsies were processed for light microscopy, and immunofluorescence according to standard techniques. No electron microscopy was performed. For each case, 8 glass slides with hematoxylin-eosin-safran (HES), periodic acid-Schiff (PAS), trichrome, and Marinozzi methenamine silver were performed. Immunofluorescence was done on 3- μ m frozen sections by use of a panel of FITC-conjugated rabbit anti-human antibodies to Fibrinogen, C3, C1q, IgG, IgM, IgA, Kappa, and Lambda light chains (Dako, Corporation). Immunofluorescence staining was graded on a scale of 0 to 3+.

2.1 Statistics

Statistical analysis utilized the logiciel Excel® and XLSTAT®. Fischer exact test or Mann Whitney test have been done according to the small number of patient for nominative variables. The t-Test has been used for quantitative variables. Patient survival was calculated by Kaplan Meier analysis using XLSTAT®.

3. Results

From the 1st of January 2000 to the 31st of December 2007, 157 patients, aged more than 70 years underwent renal biopsy; 6 were excluded because the biopsy was done on a transplanted kidney and one because it was done on a tumor, leaving a total of 150 patients.

3.1 Characteristics of the population

The mean number of kidneys biopsied was 18.7 \pm 5.4 biopsies/year. This number was quite stable with time between 2000 and 2007. Seventy eight (52%) of the patients were men and 72 (48%) were women; the mean age was 76.9 \pm 5.2 years, the range was 70 to 95 years. Kidney biopsy indications included:

- unexplained acute renal failure: 31%
- nephrotic syndrome: 30%
- rapidly progressive glomerulonephritis: 15%
- unexplained chronic renal failure: 11%
- chronic renal failure with proteinuria and/or hematuria: 8%
- proteinuria and/or hematuria with normal renal function: 5%.

3.2 Histological diagnosis

Ninety one (61%) out of the 150 patients had a glomerulopathy, 35 (23%) a tubulointerstitial nephropathy, 18 (12%) a vascular nephropathy and for 7 (4.6%) patients no diagnosis could be made (Table 1). Pauci-immune crescentic glomerulonephritis (PICGN)

with rapidly progressive renal failure (with or without nephritic syndrome) was the most common glomerulopathy (37%). Most patients with vascular nephropathy had benign nephroangiosclerosis. Finally, the leading cause of tubulointerstitial nephropathy was drug toxicity, especially after fluindione treatment (4 /13 cases).

3.3 Renal biopsy complications

Kidney biopsy was done under radiological control. Only 5 (3.3%) patients presented benign biopsy complications; two patients developed a hematoma which did not require blood transfusion, three developed a hematoma requiring blood transfusion and one had macroscopic hematuria requiring vesical lavages.

3.4 Patients with nephrotic syndrome

3.4.1 Characteristics

Forty five (30%) of the 150 elderly patients had nephrotic syndrome, defined as proteinuria more than 3g/day and serum albumin less than 30 g/L. In this group, 33% were men and 67% were women; their mean age was 77.9+/-6.13 years. Clinical characteristics are found in table 2. Patients with MCD (Minimal Change Disease) or FSGS (Focal Segmental Glomerulosclerosis) had significantly higher proteinuria than patients with MPGN (Membrano-Proliferative Glomerulonephritis) or MN (Membranous Nephropathy) (9.11g/day vs 4.61 g/day, p=0.003). Mean serum creatinine was 199 +/-166µmol/L (from 53 to 831 µmol/L) the day of biopsy; GFR estimated by MDRD was more than 60 ml/min for 14

(31%) patients, between 30 and 60 ml/min for 13 (29%) patients, between 15 and 30 ml/min for 10 (22%) patients and less than 15 ml/min for 8 (18%) patients.

3.4.2 Renal histology

The histological diagnosis of nephrotic patients (~~figure 1~~) revealed that, surprisingly, the 2 leading diagnoses were MPGN (9 patients, 20%), and MCD (9 patients, 20%) (Table 2).

All of the MPGN were type 1, all had microscopic hematuria and almost all (8 out of 9) had moderate to severe renal insufficiency. Non Hodgkin's lymphoma was the cause of the nephropathy in 3 patients, and biological cryoglobulinemia not associated with hepatitis C virus was found in 6 biopsies. The patients with MPGN did not have any underlying infectious etiology. Many patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) were identified.

All the MCD were primary and no associated neoplasia was detected during the current hospitalization or follow-up. Surprisingly, 6 out of 9 (66%) of those patients had microscopic hematuria at the time of the biopsy. In addition, 7 out of these 9 patients had both glomerular changes and significant tubulointerstitial lesions.

All the MN were idiopathic.

All 6 patients with amyloidosis had AL amyloidosis: 4 were associated with MGUS, 1 was secondary to a myeloma and one patient had Waldenstrom's disease. The kidney biopsy was done to investigate nephrotic syndrome in all of those patients and the diagnosis of amyloidosis was made with the help of the biopsy.

3.4.3 Nephrotic syndrome complications

Almost all patients (82%) had edema at the time of diagnosis and 61% had dyslipidemia. However, only 3 (6.7%) developed venous thrombosis during the follow up. All of them had MN, with serum albumin levels above 20g/L. On the contrary, several patients without MN and with serum albumin levels below 20 g/L did not have preventive anticoagulation and did not develop venous thrombosis.

3.4.4 Treatment and complications

Twenty-nine nephrotic patients were treated, there were no difference for sex ($p=0.74$), and the median age was (77.5 vs 78.5 years) between the treated and non-treated group. There was no major difference in terms of nephropathy between both groups: 6 MPGN in the treated group vs 9 in the non treated , MCD(8 vs 9), FSGS (3 vs 4) , amyloidosis (4 vs 6) and RPGN (4 vs 4) except for MN (1 vs 7).

Almost half of the patients (47%) received ACEi or ARB during follow-up to treat hypertension and/or proteinuria. As for specific glomerulonephritis treatments, 25 (86%) nephrotic patients received steroids and 64% received various immunosuppressive regimens (cyclophosphamide, cyclosporine, melphalan, gammaglobulins or rituximab) in addition to steroids (table 3). Eighteen (62%) treated patients developed therapeutic complications: 17 infections (9 bacterial, 7 viral, and one pneumocystosis), 8 psychiatric disorders, 5 bone disorders, 4 diabetes and 3 adrenal insufficiency after stopping the steroids. One death was

directly linked to treatment due to a septic shock during the period of bone marrow suppression.

3.4.5 Renal and overall Survival

Of the 29 patients treated with steroids and/or immunosuppressive drugs, 16 (55%) achieved complete remission, and 10 (34%) did not and 3 relapsed after stopping the therapy. Out of the 16 untreated patients, 4 (25%) presented with spontaneous remission, and 1 (6%) relapsed after initial spontaneous remission. In total, there was a significantly larger number of remissions after treatment ($p=0.0345$).

Renal function remained stable in 36% patients, improved in 31% and decreased in 33%, all of whom presented with severe renal failure at the time of biopsy.

At day 1000, survival was significantly better in the treated group than in the untreated group ($p=0.0227$) (figure 1). The most important factor influencing survival was initial renal function ($p=0.0042$). Interestingly, neither persistence of nephrotic syndrome nor treatment complications influenced overall survival. In addition, the mortality rate was higher in the amyloidosis group (83%) than in the MCD group (11%).

4. Discussion

This retrospective study revealed that performing renal biopsies in selected elderly patients is safe and useful in establishing a precise diagnosis for elaborating appropriate treatment strategies.

The first interesting conclusion drawn from this study, was the unusual clinical presentation of many patients, as had previously been described ^{9, 17, 18}. Many of them, except patients with amyloidosis, had high blood pressure and/or hematuria and/or renal failure, even with MCD nephropathy. MCD is thought to present as a pure nephrotic syndrome, defined by the absence of hematuria, renal failure or hypertension. Preexisting hypertension or even glomerulosclerosis can confuse the clinical presentation ¹⁹. On the other hand, 25% of MN patients did not have hematuria, which is a classical clinical symptom of MN. This statement confirms the importance of renal biopsy in the elderly for establishing a specific diagnosis and in helping direct subsequent treatment.

The second interesting finding is the presentation of those patients and their nephropathies. Some patients were more than 80, even 90 years old. The gender ratio was 33% men and 67% women, which is expected for those ages. The indication for renal biopsy resembled previous published cohorts: ~30% presented with nephrotic syndrome and 30% with acute renal failure ^{1, 2, 9, 12, 14, 17, 20}. However, the histological diagnoses were more variable. Renal drug toxicity is often thought to be a frequent cause of renal failure, especially in elderly patients, but represented only few cases in our population. We were not

able to determine if it was a rare event or if it was not an indication for renal biopsy. As RPGN is the leading cause of renal biopsy in the elderly, it was much more frequent in this elderly population than in younger patients⁹. Contrary to the literature²¹, secondary MCD and MN were rare compared to idiopathic MCD and MN even if underlying etiologies were rigorously and systematically investigated. The elevated rate of MPGN in our cohort was surprising, and contrasted with the small number reported in the literature^{1,9}. Furthermore, the MPGN patients did not have an underlying infectious etiology. Many patients with monoclonal gammopathies were identified, suggesting that MPGN due to hematologic disorders may be more frequent at least in Europe, than those due to infectious diseases.

4.3 Biopsy or not biopsy?

This study also revealed that, if contraindications are respected and indications well controlled, kidney biopsy is a simple and worthwhile tool, almost always providing a diagnosis, and is associated with few complications⁹. A diagnosis could not be histologically established in only 4.7%, and only 3.3% of the patients presented with complications most of which were minimal. It does not look that different from the general population, since life-threatening complications occur in less than 0.1% of biopsies and bleeding occurs in up to 13%, 6 to 7% needing for therapeutic interventions²².

Finally, our study suggests that aggressive therapy, even immunosuppressive therapy can be performed in old, and even very old patients, without an unacceptable rate of complications, especially infectious complications.

We understand that our study has several limits. It is a retrospective observational study but there is no large prospective nor retrospective geriatric cohort in the literature. Even the comparison between the treated and untreated groups should be carefully evaluated. First of all, the patients were carefully selected prior to biopsy, and secondly, nephrologists do not see all the elderly patients with renal disorders, even nephrotic syndrome. General practitioners may have selected the patients and referred only those aged patients with relatively good general status to the specialist. In addition, nephrologists only perform biopsies in aged patients who can bear the biopsy and a potential treatment. Most believe it is unnecessary to take the risk of biopsying a frail patient who cannot undergo post-biopsy treatment. The only conclusion to be made from the survival data is that treatment for nephropathy, even including steroids or other immunosuppressive therapy, was not deleterious for this group of selected elderly patients.

5. Conclusion

In conclusion, this study, like the recent published data of Moutzouris ¹⁵ showed that renal biopsy is feasible and may be indicated in elderly patients, as long as contra-indications are respected. Histological diagnosis is necessary to clarify a clinical situation, confused by previous co-morbidities and may help clinicians to choose the appropriate therapeutic intervention. Glomerulonephritis in the elderly is not uncommon, often difficult to diagnose without histology, and often requires specific and sometimes aggressive therapies.

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Figure legends

Table 1: Histological diagnosis for all the biopsied-patients over 70 years.

61% out of the 150 patients had a glomerulopathy, 23% a tubulointerstitial nephropathy, 12% a vascular nephropathy and for 4.6% patients no diagnosis could be made on the biopsy

Anti-GBM: anti glomerular membrane basement disease

FSGS: Focal segmental glomerulosclerosis

MCD: Minimal change disease

MN: Membranous nephropathy

MPGN: Membranoproliferative glomerulonephritis

ATN: Acute tubular necrosis

TMA: Thrombotic microangiopathie

Table 2: clinical characteristics of nephrotic patients

Patients with MCD, FSGS had significantly higher proteinuria than patients with MPGN or MN (p=0.003).

GFR : Glomerular filtration rate

MCD: Minimal change disease

FSGS: Focal segmental glomerulosclerosis

MN : Membranous nephropathy

MPGN: Membranoproliferative glomerulonephritis

PICGN: Pauci-immune crescentic glomerulonephritis

Table 3: number of treated patients and complications of treatment, according to the initial histological diagnosis. **No difference has been seen between groups.**

MCD: Minimal change disease

FSGS: Focal segmental glomerulosclerosis

MN : Membranous nephropathy

MPGN: Membranoproliferative glomerulonephritis

PICGN: Pauci-immune crescentic glomerulonephritis

