Is focal segmental glomerulosclerosis common among the elderly? *Geriatric biopsy results*

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As the overall life expectancy in the geriatric population increases, geriatric patients who have acute or chronic diseases are also living longer, and therefore, are utilizing outpatient clinics more frequently. The renal problems of the older patients are often bound to many extra-renal problems. A principal reason for this is that the glomerular filtration rate (GFR), which decreases along with aging, also decreases in cardiovascular diseases, or due to the nephrotoxic effects of drugs, which are used more frequently when treating the elderly. Diseases that are related to diabetic complications and side effects of therapeutic agents are also seen more often in this age group. Edema, when found in hypertensive patients is accepted as secondary to cardiac insufficiency, and the real incidence of renal pathology is overlooked.

Age-related kidney injury observed histologically includes marked widening of the glomerular basal membrane (GBM), expansion of the mesangial compartment, enlargement of the glomerulus, and the development of glomerulosclerosis. Glomerulosclerosis is more common among the elderly (5% at age 40, and up to 30% at age 80).[1] This is explained by the physiological and pathological senescence, and this explanation of physiological senescence has been changed by the observation of an animal model study, aging itself caused focal or global glomerulosclerosis in normotensive rats. They concluded that early podocyte damage may be a factor driving the development of glomerulosclerosis through podocyte injury.[2] Podocytes are injured in many forms of human glomerular diseases as well, and is now considered to be the major culprit for the progression of chronic kidney disease (CKD).[3] In most cases of CKD, degeneration of the nephron follows the pattern of focal segmental glomerulosclerosis (FSGS).[4] It was formerly thought to be a nonspecific glomerular change occurring in a variety of conditions (reflux, obesity) or progression of minimal change disease (MCD). Identification of podocyte proteins (nephrin, podocin) and their mutations resulted in FSGS being considered as a primary podocyte disease in recent years.

If aging is a factor driving development of FSGS through podocyte injury, by analyzing the kidney biopsies performed at our clinics over the past 8 years, we sought to clarify the reasons for kidney function disorders in older patients, and assessed the incidence of FSGS in geriatric patients.

After the opening in 2004 of the new Nephropathology unit with immunofluorescence (IF) microscopy in Antalya Training Hospital, and in 2005 in Aydin Adnan Menderes University Hospital, we were able to analyze kidney biopsies with much greater detail. From 2004 to December 2012, 745 patients underwent renal biopsy in the 2 hospitals (Antalya Training Hospital and Adnan Menderes University Hospital). The patient's characteristics that led to a biopsy included proteinuria more than 3 gr/day, and/or heavy hematuria. After approval of the protocol by the institutional review board, samples from patients aged 65 and older were included in the study. Patient data (age, gender, and relevant medical records) were extracted from the patient's files. The time of the biopsy was chosen for the value of serum albumin (gr/dl), serum creatinine (mg/dl) and proteinuria (gr/day) levels. Each sample was re-analyzed histopathologically by a pathologist who was not apprised of the diagnosis. Glomerulonephritis (GN) was classified according to Heptinstall's Pathology of the Kidney. Biopsies with fewer than 7 glomeruli (with or without glomerular obsolescence) were excluded. On the other hand, biopsies with even one glomerulus but with obvious histopathological changes, such as amyloidosis were not excluded. If the biopsy consisted of glomerulosclerosis in more than 50% of the glomeruli, it was considered as chronic glomerulonephritis (CGN). For IF findings, original pathology reports were used. Biopsies with more than 7 glomeruli but no glomerulus on any of the IF slides were excluded as well. One patient whose IF results were limited, but histopathological changes were typical for FSGS was included in the study.

During the year 2004 and 2012, 74 biopsies (9.9%) from patients aged 65 and older were extracted from the files. There were 39 male and 35 female patients. Median age was 73.52 (range: 65-86). We found that patients often had proteinuria, hematuria, or a high creatinine level. The general characteristics of

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the study population are shown in **Table 1**. The mean proteinuria level was 5.7 gr/d (range; 0.1-20); mean creatinine level was 2.7 mg/dL (range; 0.5-9.1); mean serum albumin level was 3.0 gr/dL (range; 1.1-4.8). We excluded one biopsy because it consisted only of muscle tissue and another 15 biopsies because they consisted of a limited number of glomeruli. The mean number of glomeruli was 13.7 (range: 3-30); and the mean number of obsolescent glomeruli (sclerotic glomeruli, glomerulosclerosis) was 4.0. Eleven patients (18.9%) had FSGS; 7 patients (12%) had chronic tubulointerstitial nephritis (TIN); 6 patients (10.3%) had membranous glomerulonephritis (MGN) and CGN; 5 patients (8.6%) had amyloidosis; 3 patients (5%) had membranoproliferative glomerulonephritis (MPGN) and lupus nephritis (SLE); 2 patients (3.4%) had diabetic nephropathy (DN) and immunoglobulin (Ig)A nephropathy; the rest of the 4 patients (1.7% each) had hypertensive nephropathy, myeloma cast nephropathy, light chain disease, and acute nephritis following acute pharyngitis. We have failed to reach any specific diagnosis for 9 biopsies as they had no histopathological changes by light microscopy and IF studies.

The number of kidney biopsies performed for elderly patients has increased in recent years. In 2004, we did not have kidney biopsies performed for the elderly, but in 2012 we had 28. Similar increases were also observed in other studies: when all age groups were included, the average age at biopsy was found to increase from 37-44 years in a study.[5] It was also observed that the annual biopsy average between 1975 to 1984 was 6.2, and increased to 15.1 between 1984 to 1991 in another study.[6] This increase, which was observed in our study and also in other studies did not reflect the increase of glomerulonephritis prevalence in the elderly, but rather reflected the increased clinical awareness of glomerulonephritis and leaving the explanation of urinary anomalies with extra-renal reasons.

Contrary to what is generally assumed, retrospective analyses of elderly patients revealed that the glomerular diseases other than physiological or pathological senescence are not rare, and the decrease of the kidney functions observed in the elderly is the result of primary kidney disease rather than any extra-renal causes. The disease most frequently reported for elderly patients is MGN. We found that 35 out of 58 patients (60.3%) had glomerular pathology (38% primary [MPGN, MGN, FSGS, IgA nephritis]) and 24% secondary (amyloidosis, hypertensive nephropathy (HN), SLE, light chain disease, myeloma cast nephropathy, DN). In various studies, the renal pathology detected by biopsy in the elderly, either primary or secondary differs from 60-84%.[7-9]

The decrease of the kidney functions as observed in elderly patients should not be attributed as age-related deterioration of the kidney function; in our 58 patients CGN was found in only 6 patients (10.3%). It was seen in 5.8% in one study,[5] and 8.4% in another study,[10] in which patients over age 80 were included. In a previous study[5] with 121 patients of similar age groups, only 4patients had chronic TIN (3.3%); one patient had end stage kidney disease, and all other patients had severe renal pathology. In the same study, there were control group patients younger than 65 years of age, and chronic TIN was detected at low incidence among 7 patients (2.7%).[5]

The GN prevalence observed in the elderly reveals different results. In 3 studies performed in India with 315 patients (29%), in Japan with 247 patients (17%), and in England with 1368 patients (36.6%), the most frequently observed pathology was MNG.[11-13] In 3 other studies,[7,10,14] 2 performed in Spain and one in the USA with 211 patients, the most frequently observed lesions are extra-capillary proliferation (25.8%), amyloidosis (16.9%) and pauci-immune glomerulonephritis (19%). The most common pathology detected in Turkey has been amyloidosis in 2 different studies (29% and 27.5%).[5,15] In our series, the most frequently observed glomerular pathology was FSGS (18.9%). Chronic TIN was the second and MGN (12%) and amyloidosis (8.6%) were the third most common glomerular pathology. When

Table 1 - First diagnosis within the FSGS group included in a study conducted in 2 hospitals in Turkey.

Patient number	Past medical history	First diagnosis	Last diagnosis
9	HT, venous insufficiency	Focal mesangial proliferation	FSGS
11	HT, cerebral ischemia	Focal proliferation	FSGS
12	HT	Hypertensive changes	FSGS
17	AMI back to one month	Mesangial proliferation	FSGS
21	HT, renal artery stenosis	Minimal mesangial proliferation	FSGS
34		FSGS	FSGS
35	Prostate cancer	FSGS	FSGS
36		FSGS	FSGS
41	HT, colon cancer, nephrolithiasis	Normal glomeruli, chronic TIN	FSGS
44	DM, CAD, HT	Normal glomeruli, HN	FSGS
57	Gastric lymphoma, thymoma	Normal glomeruli, chronic TIN	FSGS

FSGS - focal segmental glomerulosclerosis, AMI - acute myocardial infarction, HT - hypertension , DM - diabetes mellitus, CAD - coronary artery disease, TIN - tubulointerstitial nephritis

the differences observed between the series are grouped per the biopsy indications and clinical presentations, such differences disappear. In the group in which biopsy is performed for the acute kidney damage, we often face rapidly progressive glomerulonephritis (RPGN) and vasculitis. In this group, as expected, the creatinine levels are higher (2.9-4.28 mg/dL). In the biopsies performed for the nephrotic syndrome or proteinuria, we often face MNG. The most common biopsy indication in our study was edema and incidental proteinuria. Among the 6 patients whose biopsies had been performed for hematuria, biopsies revealed 2 cases of MPGN and 2 of IgA nephropathy. There was no glomerular pathology detected in the other 2 biopsies.

A relatively high frequency of FSGS was seen only in 2 studies (9.9% and 10.9%).[5,14] Eighteen FSGS was seen in one of them, in which FSGS had occurred in association with another disease in 16 out of 18 patients. Actually, FSGS is not a pathological entity (that is, not an immune-mediated glomerular injury), but an appearance of the glomerulus. There are primary (idiopathic) or secondary forms. A number of podocyte proteins have been identified to be mutated or deficient in the primary form of FSGS. Among the secondary forms there is increased intraglomerular pressure (as in hypertension [HT] and renal artery stenosis), reduced renal mass (as in ablation and reflux nephropathy), glomerulomegaly (as due to unilateral agenesis), ischemic renovascular disease, morbid obesity, diabetes, human immunodeficiency virus (HIV) infection, and so forth, all of which results in podocyte injury.[2] Experimental studies showed that reduced renal mass (ablation) alters glomerular hemodynamics in the kidney; there are fewer but larger glomeruli than normal. Since podocytes have limited capacity for cell division, they are forced to cover a much larger glomerular area. Together with the elevated glomerular capillary flow rates, the glomerulus prolapses through the tubular opening of the tuft, which is the only available outlet, and this is called "tip lesion" or is ruptured and forms the nidus of the segmental lesion.[16] This is the early change seen in FSGS, the tip variant.

In a study where the aging pattern was analyzed, it was shown in the animal model that old glomeruli are prone to end stage renal failure because glomerular cells, as well as podocytes contained genes whose expression changed during adult life, similar to aging vessels seen in atherosclerosis. Six out of 9 FSGS patients in our study had HT and their average proteinuria level was 6.6 gr/d (**Table 1**). Although we were not able to detect podocyte damage histopathologically, and since proteinuria levels were higher than expected in hypertensive nephropathy, we believe that our cases occurred in association with podocyte injury.

It was noticed that even in large series, the diseases such as "thin basement membrane disease," for which the diagnosis can only be made with electron microscopy (EM) are not seen. Correspondingly, in many series there are deficiencies in the histopathological examination method, that is, IF findings were not applied especially in the mesangioproliferative GN (MesPGN) category. Mesangial cells can proliferate along with a slight effect and without information on the presence or absence of immune deposition; it is not possible to exclude MCD and IgA nephropathy histopathologically. The MGN at the early stages reveal no light microscopic changes but IgG deposition which is seen only by IF, therefore MCD and non-sclerotic healthy glomeruli from FSGS patients may reveal MesPGN pattern with no IF findings. If the pathologist does not perform IF, and deposition on the glomeruli is not detected, the diagnosis would be "normal" for MCD and "MesPGN" for MCD or FSGS erroneously. In one study it was reported that IF was applied to 178 out of 247 biopsies and EM examination was added when necessary, and was stated that the number of IgA nephropathy could have been increased if IF studies were performed on all of the MesPGN cases. The total number of the cases with MesPGN and IgA nephropathy together is 39.4%, which is higher than MGN in their study. Although we did not perform EM, we explain the higher frequency of FSGS in our series by clinical presentation and by detailed pathological assessment. While the biopsies were being re-analyzed, we excluded cases without IF results, as well as with deficient/limited IF results and examined biopsies with serial section when necessary. In order to eliminate the FSGS diagnosis in a reliable manner, the tubular opening of the glomerulus was investigated in detail. A similar attempt had been undertaken in a retrospective analysis of steroid-resistant nephritic syndromes initially diagnosed as MCD, and found to have FSGS or tip lesion if serially sectioned.

In conclusion, renal biopsy in patients over 65 years of age without previous renal history and presenting with proteinuria more than 3 gr/d, and/or hematuria revealed a higher incidence of renal pathology (60.3%). Conditions that are expected in the elderly (CGN, TIN) are not frequent (less than 12%). Although our biopsy number is limited and biopsy inclusion criteria was not well drawn, our study revealed that the most common kidney pathology in the elderly was FSGS (18.9%). The diagnosis of late stage FSGS is not difficult histopathologically but patients do not benefit from the treatment at this stage and progress to end stage

kidney disease. Yet in the patients diagnosed during the early phase of FSGS, the results of the treatment are pleasing.[16] Moreover, secondary causes of FSGS require specific therapies (for example, antiretroviral therapy for HIV-associated FSGS, dietary sodium restriction for adaptive FSGS, that is, overworked glomeruli). With the improvement of the biopsy evaluation and our knowledge of podocyte biology in aging glomeruli,, before making a diagnosis like "normal," "MesPGN," or "MCD," and if kidney biopsies are examined in conjunction with IF and EM, we believe that the frequency of diagnosing FSGS will increase.

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