Rev Nefrol Dial Traspl. 2024;44(4):205-210

Familial Fibrillary Glomerulonephritis: A Rare Case with Histopathological Resemblance to Membranous Nephropathy

Glomerulonefritis fibrilar familiar: Un Caso Raro con Semejanza Histopatológica a la Nefropatía Membranosa

Neriman Sıla Koç[1], Betül Öğüt[2], Sena Gürevin[2], Özlem Öz[3], Özant Helvacı[4]

RESUMEN

La glomerulonefritis fibrilar es una forma rara de glomerulonefritis caracterizada por el depósito de fibrillas dispuestas de forma irregular en los glomérulos, lo que provoca disfunción renal. Presentamos aquí el primer caso familiar de glomerulonefritis fibrilar notificado en Turquía, destacando su parecido histopatológico con la nefropatía membranosa. Una mujer de 45 años, con antecedentes familiares de enfermedad renal, presentó edema y fue diagnosticada de glomerulonefritis fibrilar. La tinción inmunohistoquímica para DNAJB9 confirmó el diagnóstico. La revisión de la literatura reveló sólo seis familias con glomerulonefritis fibrilar familiar, lo que sugiere un posible patrón de herencia autosómico dominante. En comparación con los casos anteriores, nuestra paciente y los miembros afectados de la familia son mujeres y se les diagnosticó entre los 40 y los 50 años. El tratamiento de la paciente consiste en el bloqueo de los receptores de angiotensina debido a una proteinuria no nefrótica y una función renal normal. El pronóstico de la glomerulonefritis fibrilar es malo y las opciones terapéuticas son limitadas. La investigación futura debe centrarse en comprender las bases genéticas de la glomerulonefritis fibrilar familiar y desarrollar tratamientos eficaces. Este caso subraya la importancia de considerar la glomerulonefritis fibrilar en el diagnóstico diferencial de la glomerulonefritis, especialmente en los casos familiares, y destaca la necesidad de realizar más estudios para mejorar su tratamiento.

Palabras clave: Glomerulonefritis Fibrilar Familiar, Nefropatía Membranosa

ABSTRACT

Fibrillary glomerulonephritis is a rare form of glomerulonephritis, characterized by the deposition of haphazardly arranged fibrils in the glomeruli, leading to renal dysfunction. Here, we present the first familial case of fibrillary glomerulonephritis reported from Türkiye, highlighting its histopathological resemblance to membranous nephropathy. A 45-year-old female with a family history of kidney disease presented with edema and was diagnosed with fibrillary glomerulonephritis. Immunohistochemical staining for

Correspondencia:
Neriman Sıla Koç
ORCID:
0000-0002-4654-9002
silacank@hotmail.com

Financiamiento:
Ninguno.

Conflicto de intereses:
Ninguno que declarar.

Recibido: 12-07-2024
Corregido: 24 -10-2024
Aceptado: 01-11-2024

1) Harran University Medical Faculty, Department of Internal Medicine, Division of Nephrology, Şanlıurfa
2) Gazi University Medical Faculty, Department of Pathology, Ankara
3) Harran University Medical Faculty, Department of Genetics, Şanlıurfa
4) Gazi University Medical Faculty, Department of Internal Medicine, Division of Nephrology, Ankara

DNAJB9 confirmed the diagnosis. The literature review revealed only six reported families with familial fibrillary glomerulonephritis, suggesting a possible autosomal dominant inheritance pattern. Compared to previous cases, our patient and affected family members are female and diagnosed at ages 40-50. The patient's treatment involves angiotensin receptor blockade due to non-nephrotic proteinuria and normal renal function. The prognosis for fibrillary glomerulonephritis is poor, and therapeutic options are limited. Future research should focus on understanding the genetic basis of familial fibrillary glomerulonephritis and developing effective treatments. This case underscores the importance of considering fibrillary glomerulonephritis in the differential diagnosis of glomerulonephritis, especially in familial cases, and highlights the need for further studies to improve its management.

Keywords: Familial Fibrillary Glomerulonephritis, Membranous Nephropathy

INTRODUCTION

Fibrillary glomerulonephritis (FGN) is a rare form of glomerulonephritis, accounting for less than 1% of native kidney biopsies [1]. FGN typically presents with proteinuria, hematuria, and hypertension, mainly affecting middle-aged or older adults, with a higher incidence in females. FGN is characterized by non-branching fibrils (15-25 nm) in glomerular capillary walls and/or mesangium without congo red reactivity [2]. Immunoglobulin G (IgG) and C3 are dominant intraglomerular depositions. Identifying DNAJ homolog subfamily B member 9 (DNAJB9) as a marker has improved diagnosis [3].

Patients often present with microscopic hematuria, proteinuria, hypertension, and sometimes nephrotic syndrome. FGN may be primary or secondary to systemic illnesses such as hepatitis B and C, autoimmune disorders, cancer, diabetes mellitus, and monoclonal gammopathy. Familial clustering is rare, with only six families reported.

We present the first case of familial FGN from Türkiye, histopathologically mimicking membranous nephropathy, and review the literature on familial FGN.

Case

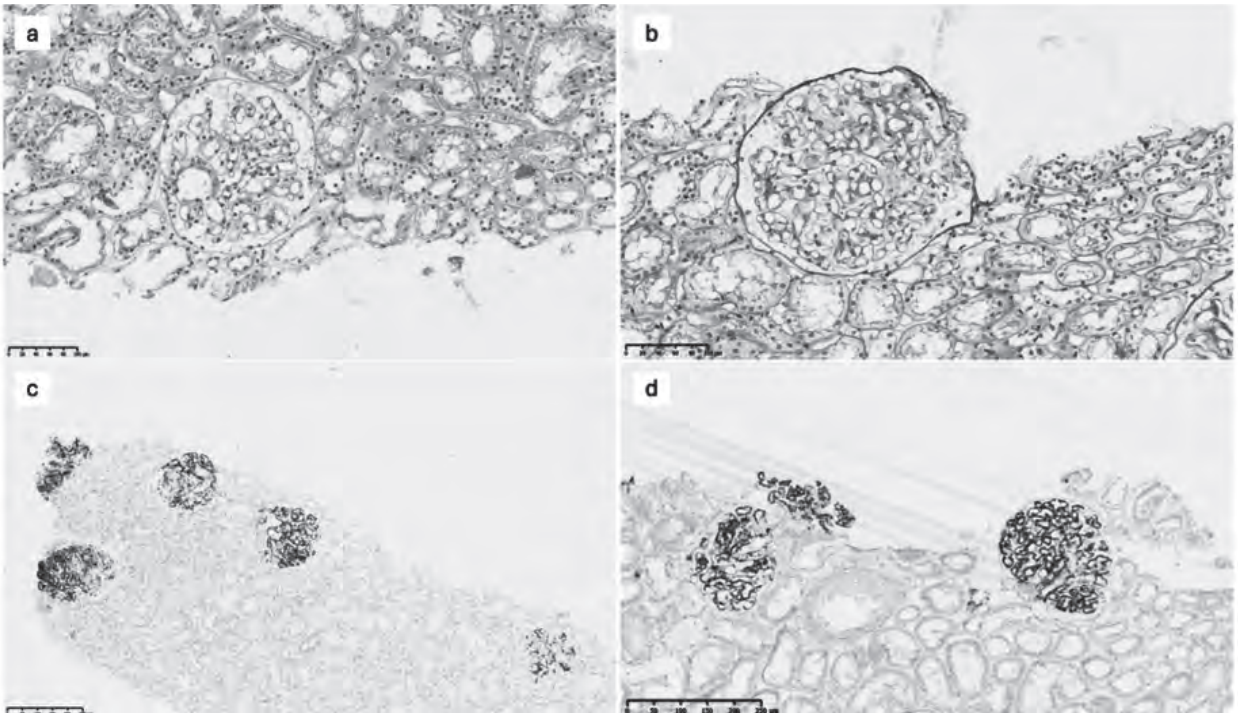
A 45-year-old non-diabetic was consulted at the hospital with lower extremity edema. The patient had hypothyroidism and a history of brucella infection 20 years ago. Laboratory results showed 1.8 g proteinuria in 24-hour urine, albumin 3.8 g/dL, creatinine 0.6 mg/dL, and an estimated GFR of 110 mL/min/1.73 m². Other parameters were unremarkable.

The patient reported a family history of kidney disease, with her mother and sister undergoing hemodialysis of unknown etiology. Physical examination revealed a blood pressure of 170/90 mmHg, afebrile status, and bilateral pretibial edema.

Urine studies showed microscopic hematuria and proteinuria (1552 mg/24 hours albuminuria, 1800 mg/24 hours proteinuria). Renal ultrasound indicated mildly reduced cortical thickness and grade 1 increased cortical echogenicity. Additional tests (Hemoglobin A1C, complement, hepatitis C antibody, HIV antibody, ANA, ASO, anti-dsDNA, cANCA, pANCA, anti-GBM, and HbsAg) were in the normal range or negative. Serum immunofixation detected no monoclonal protein, and genomic analysis for Fabry disease was negative.

In the kidney biopsy, 33 glomeruli were examined under light microscopy, with two [2] glomeruli separated for immunofluorescence (IF). Light microscopy revealed two globally sclerosed glomeruli. Among the non-sclerotic glomeruli, mild to moderate mesangial expansion was accompanied by mild mesangial proliferation and focal extensive thickening of the glomerular basement membrane (GBM). Interstitial fibrosis and tubular atrophy were absent, but mild interstitial inflammation was noted. Renal vasculature appeared normal. Congo red staining yielded negative results. Immunofluorescence analysis showed the presence of 3+ IgG,+2 κ-chain, and +2 λ-chain immune depositions on the glomerular membrane and mesangium in a granular pattern. Mild thickening was observed in tubular basal membranes (TBM). The diagnosis of FGN was definitively confirmed through immunohistochemical staining for DNAJB9, which exhibited strong positivity along the GBM, segmentally in the mesangium and TBMs
(**Figure 1**).

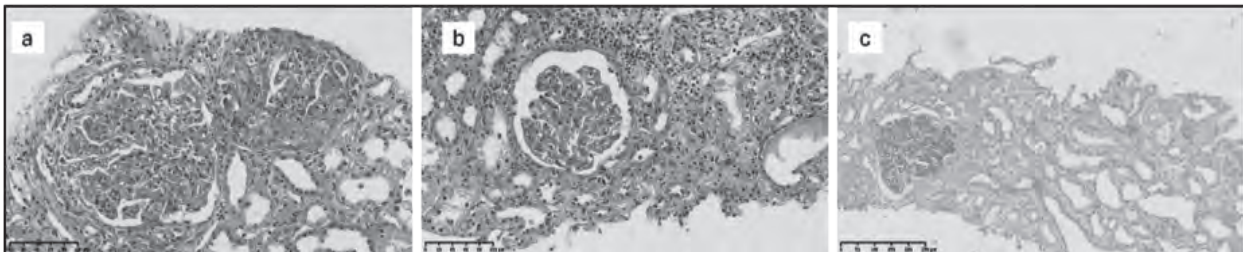
Figure 1: Microscopic appearance of glomeruli



***A, B**: Diffuse thickening of glomeruli's capillary walls, resembling membranous nephropathy (H&E and PAS stains, x400). **C:** Strong expression of C4d on all glomerli's capillary walls (Immunoperoxidase stain for C4d, x200). **D:** DNAJB9 expression on glomerular capillaries and mesangial matrix (Immunoperoxidase stain for DNAJB9, x200)*

Eight years ago, the patient's older sister applied to another center due to deterioration in her kidney functions. A kidney biopsy was performed and revealed a total of four glomeruli. Hematoxylin and eosin (H&E) staining showed inflammatory cells present in the capillary lumens of the glomeruli. An increased mesangial matrix and irregular thickening of the capillary walls were also noted. One glomerulus exhibited extracapillary proliferation and cellular crescent formation. The patient's renal functions quickly progressed to end-stage renal disease, and the patient has been followed up with hemodialysis treatment since then. After our patient was diagnosed with fibrillar GN, her sister's paraffin blocks were re-evaluated to be stained for DNAJB9. Immunohistochemical analysis of the biopsy demonstrated diffuse expression of DNAJB9
(**Figure 2**).

Figure 2: Microscopic appearance of glomeruli



***A, B**: Thickening of glomeruli's capillary walls, increased mesangial matrix. In one glomerulus, cellular crescent was observed (H&E, x200). **C:** DNAJB9 expression on glomerular capillaries and mesangial matrix (Immunoperoxidase stain for DNAJB9, x200)*

Her mother had a similar history, but without a kidney biopsy, she was diagnosed with end-stage chronic kidney disease and started hemodialysis.

Since the patient's mother and sister had a history of end-stage renal disease, it was thought that she might have familial fibrillar glomerulonephritis and a genetic test was sent, but no significant genetic mutation was detected. The patient's family pedigree is shown in **Figure 3**.

Pedigree contains four generations of family. Besides her sister, the proband's mother and four brothers of grandmother have a possible diagnosis of fibrillar glomerulonephritis.

Treatment with 50 mg of losartan potassium, increased to 100 mg daily, reduced proteinuria from 1800 mg/day to 760 mg/day. Efforts are ongoing to resolve reimbursement by adding an SGLT-2 inhibitor.

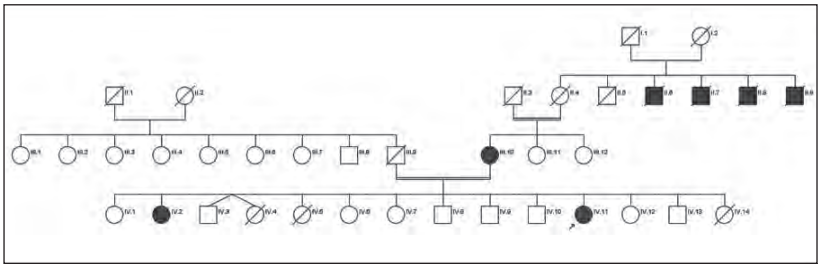


Figure 3: Family pedigree of the patient

DISCUSSION

FGN is a rare immune-mediated glomerular disease. Histologically, it presents extensive mesangial matrix enlargement and the thickening of glomerular basement membranes due to deposits, defining FGN. To our knowledge, familial FGN has been reported in 6 families in the literature (**Table 1**).

Table 1: Published cases of familial fibrillary glomerulonephritis

Authors, year	Subjects	Age at diagnosis	Symptom	Pathology EM (Fibril,nm)	Pathology DNAJB9	Treatment
Chan et al.,1998	Sister	36	Proteinuria	20-30	N/A	F
	Brother	38	Proteinuria	20-30	N/A	F
Ying et al.,2015	Father	64	İmpaired renal function	10-15	N/A	F
	Daughter	43	Proteinuria, hematuria	10-15	N/A	ESRD
Ying et al.,2015	Mother	61	NS	15	N/A	ESRD
	Son	40	NS	N/A	N/A	F
Watanabe et al.,2017	Brother	35	Proteinuria	N/A	N/A	F
	Older brother	40	Proteinuria	20	N/A	F
	Father	N/A	N/A	N/A	N/A	N/A
Andeen et al.,2019	Mother	N/A	N/A	N/A	N/A	ESRD- N/A
	Daughter	N/A	N/A	N/A	+	ESRD- N/A
Jeyabalan et al.,2020	Father	49	Proteinuria	16	+	Preemptive tx
	Son	35	Asymptomatic	18	+	F
Koc et al.,2024	Daughter*	45	Proteinuria	N/A	+	F
	Daughter	50	İmpaired renal function	N/A	+	ESRD-HD
	Mother	62	İmpaired renal function	N/A	N/A	ESRD-HD

: Our index case,* ***ESRD**: End stage renal disease,* ***F****: Following,* ***HD****: Hemodialysis,* ***N/A****: Not available,* ***TX****: Transplantation*

 ISSN 0326-3428

Our case is the first diagnosed member of the FGN family published from Türkiye. It also attracts attention due to its similarity to membranous nephropathy in light microscopy.

More knowledge of the pathophysiology of FGN is needed. Even though FGN is frequently idiopathic in origin, it can also have secondary causes, including cancer, autoimmune disorders, and hepatitis C infection [4]. Meanwhile, recent research has demonstrated a relationship between FGN and the HLA-DR7 and HLA-B35 antigens [5].

The first familial FGN that affected a brother, and a sister was reported in a Chinese family in 1998 [6]. Then, two families from Australia (father and daughter, mother and son) were reported [7]. In 2017, a male patient with a biopsy-proven diagnosis of FGN and whose brother and father were diagnosed with nephrotic syndrome were presented [8].

In a 2019 study, Andeen et al. evaluated 296 kidney biopsies retrospectively, and two patients were mother and daughter [9].

Finally, in 2021, in another family, his son, who was a kidney donor to his father, who had Gna, was found to have FGN in the intraoperative kidney biopsy. However, a successful transplant was performed, and it was reported that the recipient was observed with moderate proteinuria during approximately two years of follow-up [10].

In patients with FGN, various histologic types of glomerular damage such as diffuse proliferative glomerulonephritis, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, membranous glomerulonephritis, have been reported [11]. More recent research suggests that IgG1 and IgG4 are present in FGN, contrary to the first description of immune deposits as IgG4 predominating [2]. A case like RPGN with a poor prognosis and no response to treatment has been reported in the literature, as in our patient's sister [12]. Our patient's kidney biopsy detected diffuse membranous thickening across all glomeruli. Increased mesangial matrix was observed alongside membranous thickening in only three glomeruli.

Moreover, spike formations on the GBM were absent in the methenamine silver stain. These findings prompted our nephropathologists to consider fibrillar glomerulonephritis. However, upon reviewing the immunofluorescent findings, the kidney biopsy results closely resembled those of membranous glomerulonephritis. Therefore, our case will significantly contribute to the literature by highlighting the importance of considering fibrillar glomerulonephritis, which exhibits morphological similarities to membranous nephropathy but does not entirely overlap.

A case report also highlights that light microscopy can mimic membranous glomerulopathy stages III-IV, especially when examining a small kidney sample with extensive involvement by GBM fibrils [13]. In this case, the diagnosis was confirmed by observing randomly assigned fibrils in the mesangium and glomerular membrane on electron microscopy and immunohistochemical staining for DNAJB9. The patient achieved an 85% reduction in proteinuria with steroids, rituximab, and dapagliflozin. Our patient is also being followed closely with angiotensin receptor blockade.

Before the discovery of DNAJB9 in 2018, cases were diagnosed by seeing randomly arranged fibrils of 10-30 nm in size in electron microscopy. After this date, the use of DNAJB9 came to the fore. In our case, there was no need to evaluate electron microscopy due to DNAJB9 positivity.

When the few familial FGN cases in the literature were examined, the diversity of hereditary pathways was noted, and an autosomal dominant genetic type was suspected. Considering our case and the patients in the family through pedigree analysis, it is seen that the disease is transmitted by autosomal dominant inheritance, especially since there are affected individuals in each generation. Although the presence of consanguineous marriage between both the patient's mother and father and between the patient's grandparents brings to mind autosomal recessive transmission, the fact that the disease was not observed in individuals on the paternal side eliminates this possibility. Familial FGN patients in the literature showed that the condition primarily affected men and those aged 35 to 65 [6-8,10]. Our patient and the affected patients in her family are female patients diagnosed between the ages of 40-50. In addition, the brother of the patient's grandmother died at an earlier age, at the age of 56-60, and required dialysis.

With few therapeutic options available, the prognosis for FGN is very poor. The most critical markers affecting prognosis are baseline serum creatinine, age, 24-hour urine protein, and degree of glomerulosclerosis [2].

There are no established protocols for the care of FGN patients. If someone has a secondary cause of FGN, finding and treating it is critical. The severity of the renal illness dictates the approach. The conservative treatment of proteinuria with less than 3.5 g/day and GFR of more than 60 ml/min/1.73 m2 should involve anti-proteinuric drugs like angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Treatment is unclear for patients whose GFR is less than 60 ml/min/1.73 m2 and whose proteinuria exceeds 3.5 g/day. Although no noteworthy trials have been investigated, immunosuppressive drugs may be employed as a treatment approach. Steroids, mycophenolate mofetil (MMF), cyclophosphamide, and cyclosporine have all been taken up to this point without seeming to help [14].

Since IgG makes up most of the glomerular deposits, rituximab, an anti-CD 20 monoclonal antibody, was introduced as a viable treatment for anti-B cell therapy. It has been shown to slow the process without appreciably altering proteinuria [1,9,15]. Our patient is being monitored conservatively with angiotensin receptor blockade due to her non-nephrotic proteinuria and normal glomerular filtration rate.

CONCLUSION

This present case is the first incidental case of familial FGN seen in Türkiye. It is also important because FGN is similar histopathologically to membranous nephropathy.

Conflict of Interest Statement: All authors had no separate personal, financial, commercial, or academic conflicts of interest.
Ethics Statement: Not applicable.
Inform Consent: The patient gave consent for publication.

BIBLIOGRAPHY

1) Erickson SB, Zand L, Nasr SH, Alexander MP, Leung N, Drosou ME, et al. Treatment of fibrillary glomerulonephritis with rituximab: a 12-month pilot study. *Nephrol Dial Transplant*. 2021;36(1):104-10.
2) Rosenstock JL, Markowitz GS. Fibrillary Glomerulonephritis: An Update. *Kidney Int Rep*. 2019;4(7):917-22.
3) Andeen NK, Yang HY, Dai DF, MacCoss MJ, Smith KD. DnaJ Homolog Subfamily B Member 9 Is a Putative Autoantigen in Fibrillary GN. *J Am Soc Nephrol*. 2018;29(1):231-9.
4) Nasr SH, Vrana JA, Dasari S, Bridoux F, Fidler ME, Kaaki S, et al. DNAJB9 Is a Specific Immunohistochemical Marker for Fibrillary Glomerulonephritis. *Kidney Int Rep*. 2018;3(1):56-64.
5) Andeen NK, Smith KD, Vasilescu ER, Batal I. Fibrillary Glomerulonephritis Is Associated With HLA-DR7 and HLA-B35 Antigens. *Kidney Int Rep*. 2020;5(8):1325-7.
6) Chan TM, Chan KW. Fibrillary glomerulonephritis in siblings. *Am J Kidney Dis*. 1998;31(5):E4.
7) Ying T, Hill P, Desmond M, Agar J, Mallett A. Fibrillary glomerulonephritis: An apparent familial form? *Nephrology (Carlton)*. 2015;20(7):506-9.
8) Watanabe K, Nakai K, Hosokawa N, Watanabe S, Kono K, Goto S, et al. A Case of Fibrillary Glomerulonephritis with Fibril Deposition in the Arteriolar Wall and a Family History of Renal Disease. *Case Rep Nephrol Dial*. 2017(1):26-33.
9) Andeen NK, Troxell ML, Riazy M, Avasare RS, Lapasia J, Jefferson JA, et al. Fibrillary Glomerulonephritis: Clinicopathologic Features and Atypical Cases from a Multi-Institutional Cohort. *Clin J Am Soc Nephrol*. 2019;14(12):1741-50.
10) Jeyabalan A, Batal I, Piras D, Morris HK, Appel GB. Familial Fibrillary Glomerulonephritis in Living Related Kidney Transplantation. *Kidney Int Rep*. 2021;6(1):239-42.
11) Rosenstock JL, Markowitz GS, Valeri AM, Sacchi G, Appel GB, D'Agati VD. Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features. *Kidney Int*. 2003;63(4):1450-61.
12) Raikar M, Shafiq A. Fibrillary Glomerulonephritis: A Great Mimicker of Rapidly Progressive Glomerulonephritis. *Cureus*. 2022;14(6):e26001.
13) Sabanis N, Liaveri P, Geladari V, Liapis G, Moustakas G. DNAJB9 Fibrillary Glomerulonephritis with Membranous-Like Pattern: A Case-Based Literature Review. *Cureus*. 2023;15(10):e47862.
14) Javaugue V, Karras A, Glowacki F, McGregor B, Lacombe C, Goujon JM, et al. Long-term kidney disease outcomes in fibrillary glomerulonephritis: a case series of 27 patients. *Am J Kidney Dis*. 2013;62(4):679-90.
15) Hogan J, Restivo M, Canetta PA, Herlitz LC, Radhakrishnan J, Appel GB, et al. Rituximab treatment for fibrillary glomerulonephritis. *Nephrol Dial Transplant*. 2014;29(10):1925-31.