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Renal involvement in familial Mediterranean fever in an Algerian population

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Key words
nephrotic syndrome – consanguinity – AA amyloidosis – familial Mediterranean fever

Abstract. The objectives of this study were to investigate the clinical biological and histological renal involvement secondary to familial Mediterranean fever (FMF), the epidemiological data, genetics of our patients and their evolution under treatment. We prospectively studied 58 Algerian patients admitted in our nephrology department from January 2012 to January 2021. The diagnosis of nephropathy was suspected clinically and biologically and confirmed histologically. All our patients were tested for *MEFV* mutations. Results: 58 patients, 30 males and 28 females, mean age 31.68 ± 12.71; 3 (5.17%) chronic dialysis patients and 55 (94.82%) referred to the nephrology department for renal biopsy with renal symptomatology consisting of nephrotic syndrome in 50 (94. 73%), associated with renal failure 27 (47.36%), mainly primary in 23 (34.5%), secondary to seronegative lupus 13 (22.4%), Crohn's disease 9 (14.5%), sarcoidosis 3 (5.26%), and lymphoma 1 (1.7%); 29 (50%) were from consanguineous marriages, the histological study found AA amyloidosis in 52 (89.6%); the genetic study confirmed the diagnosis of FMF in 58 (100%). **Evolution of our patients under colchicine alone:** 45 (77.6%) patients were alive and followed up, 25 (43.1%) of them were on dialysis and 13 (22.4%) died **[■■■ Please check changes we tried to make for clarity]**. Conclusion: Renal involvement was the revealing complication in the diagnosis of FMF which exists in our country, and is still underdiagnosed.

Introduction

Familial Mediterranean fever (FMF; OMIM #249100) is the most common form of autoinflammatory genetic disease in the world. Affected patients usually carry mutations in the *Mediterranean fever (MEFV)* gene, which is usually autosomal recessive. The disease mainly affects populations of Mediterranean origin. Clinically, the disease manifests early in life with recurrent episodes of sterile systemic inflammation in the form of episodes of febrile peritonitis, pleuritis, and arthritis [1]. The *MEFV*

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gene responsible for FMF was discovered in 1997 [2]. Amyloidosis secondary to FMF is a condition that is said to be rare or even non-existent in our country [3]; this condition is unknown to our colleagues and nephrologists, which places FMF **among the causes of idiopathic AA amyloidosis [■■■ Please check changes.]** [3]. The most frequent cause of renal amyloidosis in Algeria is pulmonary and extrapulmonary tuberculosis [3]. We recently became interested in this pathology because Algerian geneticists have started working on *MEFV*, and all suspect patients were tested. Our hypothesis that FMF exist in our country was correct as most of the patients sampled had homozygous or heterozygous mutation [4].

Materials and methods

AA amyloid nephropathy in FMF usually progresses over several years to end-stage renal disease (ESRD). Our objective was to describe the secondary nephropathy of FMF as well as the factors involved in the renal and overall survival of these patients. This prospective analysis included data from January 2012 to January 2021 on 58 adult and pediatric patients with FMF secondary nephropathy, and for each patient we studied epidemiological data (age, sex, consanguinity), the diagnoses made by their original physicians, the age of onset of renal symptoms, the factors triggering and/or preceding renal involvement, renal symptomatology at the time of tissue biopsy was assessed by the degree of proteinuria (g/24h), the presence of an active urine sediment (> 5 high-powered red blood cells/field and/or cell blasts on urine microscopy), serum creatinine level. Glomerular filtration rate was calculated using the formulas Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault, the ESRD being defined as a glomerular filtration rate < 15 mL/min/1.73/m^2. The presence of high blood pressure (HBP) was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Biologically, nephrotic syndrome was defined as a level of albuminemia < 30 g/L associated with a proteinuria > 3 g/24h, C-reactive protein (CRP) positive with a rate > 5 g/L. The identification of nephropathy was done using renal biopsy or salivary gland biopsy and read by the same experienced pathologist. After trichrome Masson staining seen under light microscopy (LM), if amyloidosis deposits were suspected, she combined with red Congo stain, which was seen under light polarized microscope, she completed the examination by anti-SAA immunohistochemistry, and she finished after that by immunofluorescence (IF) which was systematically done for antiserums: IgA, IgM, IgG, IgA, light chain λ and κ. These patients who **received a histological** diagnosis of AA amyloidosis **[■■■ Please check changes.]** were then hospitalized again for the search of extra-renal signs of systemic amyloidosis (goiter, diarrhea, melanoderma, etc.), a cervical ultrasound was made, and we concluded amyloid hypothyroidism if the levels of thyroid-stimulating hormone (TSH) were greater than 10 mUI/L with T3 ≤ 9 µmol/L and T4 ≤ 0.6 ng/L . After eliminating other causes of AA amyloidosis, the clinical diagnosis of FMF was established on the basis of the Tel Hashomer criteria and genetically confirmed. The *MEFV* gene sequenced on exon 10 only by PCR was checked for alleles (M694I, M694V, M680I) in the period between 2012 and 2015, on exons 1 – 10 in another private laboratory in the period between 2016 and 2021, all patients with no mutation found were not **collected** in this study **[■■■ What do you mean be collected? It cannot be the correct word here. Do you mean "included"?]**. All patients were treated with colchicine except for patients with renal contraindication: creatinine Cl < 30 mL/min. For statistical analysis, SPSS version 25.0 software (SPSS, Chicago, IL, USA) was used. Basic descriptive statistics, χ^2-test and Mann-Whitney U test for group comparison, Cox regression analysis were also performed. All data are presented as mean ± SD. A relationship was considered statistically significant at p-values < 0.05.

Results

Patients were referred to our department for the feasibility of kidney biopsy by various departments of our hospital and surrounding hospitals, 58 patients (30 males and 28 females), mean age 31.7 ± 12.86 years age limits (6 – 60 years), they were recruited by our department: 55 for renal biopsy, and the 3 other are chronic dialysis

Table 1. Triggers and diagnoses for renal symptomatology.

Parameters	n (%)
M/F sex and sex ratio	30/28, 1.07
Average age of onset of kidney damage	31.77 ± 12.867 (6 – 60)
Diagnoses mentioned by the doctors of origin	
Primitive	23 (39.65)
Lupus	13 (22.4)
Lymphoma	1 (1.7)
Crohn's disease	9 (15.5)
Sarcoidosis	3 (5.17)
Triggering factors for kidney damage	
Surgical procedure	7 (12.06)
Infectious process	22 (37.9)
Taking medication	1 (1.7)

Table 2. Clinical and histological signs of renal involvement in patients.

Parameters	Results n (%)
Renal functional signs	
Nephrotic syndrome	54 (94.1)
Polyuro-polydipsic syndrome	1 (1.7)
Isolated proteinuria	0
Microscopic hematuria	7 (12)
Glucosuria	2 (3.5)
RPGN	9 (15.5)
HBP	12 (20.6)
Renal failure	27 (46.5)
CKD1	5 (8.77)
CKD2	4 (6.9)
CKD3 (A+B)	4 (6) 94
CKD4	14 (24.1)
CKD5	3 (5.1)
Chronic dialysis patients	
Biopsy site	
Renal	54 (94.1)
Salivary gland	3 (5.1)
Histological type	
AA amyloidosis	52 (89.65)
glomerular deposits	48 (82.7)
tubulointerstitial deposits	15 (25.8)
vascular vessel deposits	24 (41.37)
IgA nephropathy	2 (3.5)
Minimal change disease	2 (3.5)
Membranoproliferative glomerulonephritis	2 (3.5)
Number of sclerosed glomeruli > 50%.	17 (29.3)
Extra-renal signs of AA amyloidosis	
Thyroid	18 (31)
Adrenal gland	2 (3.5)
Digestive	12 (20.6)
Pulmonary	2 (3.5)
Splenic	2 (3.5)
Hepatic	2 (3.5)

RPGN = rapidly progressive glomerulonephritis; HBP = high blood pressure; CKD = chronic kidney disease.

patients hospitalized for pre-transplant assessment (1 (1.7%)), arteriovenous fistula (1 (1.7%)), and abdominal pain in a chronic dialysis patient (1 (1.7%))); the most common trigger for kidney injury was infectious process in 29 (37.9%). None of these patients had an accurate diagnosis of the causal disease (Table 1), but AA amyloid nephropathy was suggested in most cases. The most common nephrological clinical sign was nephrotic syndrome in 54 (94.73%) of our patients, HBP in 12 (20.68%), microscopic hematuria in 7 (12%), renal failure in 58 (100%), rapidly progressive glomerulonephritis (RPGN) in 9 (15.5%) which required corticosteroid bolus, 3 patients in their home departments and 6 patients in our department (anatomopathology gives an emergency result within 21 days after biopsy). The most frequently found extra-renal symptoms were thyroid disorders diagnosed with the clinical and ultrasound presence of a goiter in 10 (17.4%) and found biologically in 8 (13.8%), and digestive disorders were present in 12 (20.7%) clinically with the presence of mucous diarrhea; lung, hepatic, splenic, and adrenal disorders were seen in dialysis patients only (Table 2).

For histological results, we had 52 patients with AA amyloidosis and 6 patients with other nephropathies: 2 (3.44%) minimal glomerular changes, 2 (3.44%) membranoproliferative glomerulonephritis, 2 (3.44%) IgA nephropathy, glomerular amyloid deposits were present in most of our patients (48 (82.75%)), tubulointerstitial in 15 (25.86%) and perivascular in 24 (41.4%); 14 of the patients (24.13%) had a number of sclerosed glomeruli > 50% and 34 (58.6%) had a number of sclerosed glomeruli < 50% (Table 2).

Interrogation revealed that 29 (50%) patients had consanguineous parents and had clinical signs of FMF since they were young and went from one specialist to another and no one made the diagnosis of this disease or the link with renal involvement because it was not well known by our colleagues. 10 (17.24%) patients described similar cases in their families, the mean age of onset of these attacks was 10.82 ± 5.91 years; 10 (17.24%) patients described seizures with a monthly periodicity < 1/month, 17 (29.3%) had between 1 and 2 seizures per month, and 31 (53.44) patients had > 2 seizures/month. 38 (65.61%) patients were on colchi-

Table 3. Clinical features of familial Mediterranean fever in our patients.

Parameters	n (%)
Average time in years between kidney damage and FMF	20.82 ± 10.652
Consanguinity	29 (50)
Other FMF cases in the family"	10 (17.54)
Age at first FMF attack (average age)	10.82 ± 5.91
Number of attacks/month	
< 1	10 (17.2)
1 – 2	17 (29.3)
> 2	31 (53.4)
Clinical signs of FMF	
Fever	58 (100)
Abdominal pain	43 (74.1)
Arthralgia	43 (74.1)
Arthritis	6 (10.3)
Destructive sacroiliitis (radiology)	3 (5.1)
Erysipelas-like exanthema	10 (17.52)
Pleuritis	9 (15.5)
Headaches	30 (51.7))
Oral aphthosis	20 (34.4))
Unilateral orchitis	1 (1.7)
Myalgias	30 (51.7)
Appendectomy	6 (10.3)

FMF = familial Mediterranean fever.

Table 4. Patient genotypes, number of alleles, frequency and distribution of mutations.

Status	Genotype	Patients N = 58 n (%)
	M694I/M694I	30 (51.7)
	M694V/M694V	4 (6.9)
Homozygous	M680I/M680I	1 (1.7)
Compound heterozygous	M694I/M694V	4 (6.9
	M694V/I692Del	2 (3.4)
	M694I/M680I	1 (1.7)
	V726A/E148Q	2 (3.4)
	V726A/I692Del/E148	2 (3.4)
Heterozygous	K695R/WT	1 (1.7)
	M694I/WT	8 (13.7)
	V691A/WT	1 (1.7)
	E148Q/WT	1 (1.7)
	M694V/WT	1 (1.7)
Number of patient alleles		104 (100)

cine of which 5 (8.62%) were on dialysis, but 5 (8.62%) were resistant to colchicine. The clinical features are described in Table 3.

Regarding genetic results, the most frequent mutation in our patients was M694I in the homozygous state (29 (50.87%)), M694V in the homozygous state is the mutation exclusively observed in dialysis patients. The genotypes of the patients, the number of alleles, the frequency and the distribution of the mutations in our patients are described in Table 4.

We followed all these patients over a period of 9 years, 24 patients progressed to CKD, and 33 were followed in nephrology consultation. The response to colchicine is detailed in Table 3. The 33 patients have a regular follow-up in consultation, 29 (87.87%) had a complete response for those with renal failure < 15 mg/L serum creatinine (25 CKD1, 3 CKD2, and 1 CKD3A) with good renal evolution: proteinuria under 1 g/24h without clinical signs of FMF under colchicine therapy combined antiproteinurics drugs; but only 4 (12.12%) were resistant to colchicine and died from the consequences of FMF, and systemic amyloidosis associated with kidney damage (nephrotic syndrome), but with good renal function: 1 (1.75%) after surgery for acute intestinal obstruction, 1 (1.75%) pulmonary embolism, 1 (1.75%) myocardial infarction, 1 (1.75%) acute adrenal insufficiency associated with hyperkalemia.

Of the patients on dialysis, 3 (5%) had CKD3B, 4 (6, 9%) had CKD4, 14 (24%) had CKD5, 3 (5%) were started on dialysis; the 7 patients on colchicine progressed to need for dialysis, 4 (7%) suffered from prolonged dehydration after fasting during Ramadan, 2 (3.4%) after infection, and 1 (1.7%) had rhabdomyolysis secondary to an overdose of colchicine. On hemodialysis, 20 had a disappearance of FMF signs, but 4 (with triggers such as menses, surgery, after: arteriovenous fistula, catheter placement, and COVID-19 infection) continued to take colchicine, 3 (5%) with a good response and 1 (1.7%) was resistant to colchicine; 9 (15.78%) patients died on dialysis: 3 (5%) diarrhea malnutrition, 2 (3.4%) acute lung edema, 1 (1.7%) atrioventricular block, 1 (1.7%) digestive hemorrhage, 2 (3.4%) undetermined origin; 3 (5%) of the chronic dialysis patients received a transplant from related living donors, and all repients were under colchicine (Table 5).

Cox regression analysis with at any time calculation of risk of death from the date of hospitalization log-likelihood test -2 = 160.382 with $p < 10^{-3}$ was statistically significant. Cox regression analysis with calculation at any time of the risk of death from the date of hospitalization the log-likelihood

Table 5. Patients' characteristics.

Parameters	N = 58 n (%)
Men	30 (51.7)
Women	28 (48.27)
Average age of onset of kidney damage	31.68 ± 12.71
Average age of onset of FMF	10.82 ± 5.91
Triggering factors for kidney damage	32 (55.17)
HBP	12 (20.68)
Mean serum albumin level g/L	17.25 ± 5.25
Average proteinuria rate g/24h	7.72 ± 4.74
CRP rate	56.12 ± 42.23
Average serum creatinine g/L	29.12 ± 36.96
Hematuria	14 (24.13)
RPGN	9 (**15.%7**) **[■■■ "15.7"?]**
AA amyloidosis	52 (89.65)
Other kidney diseases	6 (10.34)
Glomerular sclerosis > 50%.	17 (29.3)
Extarenal involvement in AA amyloidosis	38 (65.51)
Homozygous and/or compound heterozygous	46 (79.3)
Heterozygous	12 (20.68)
Living patients	45 (77.58)
In dialysis	25 (43.1)
Patients who died	13 (22.4)
Number of days of survival	2,242.67 ± 1,612.997

FMF = familial Mediterranean fever; HBP = high blood pressure; CRP = C-reactive protein; RPGN = rapidly progressive glomerulonephritis.

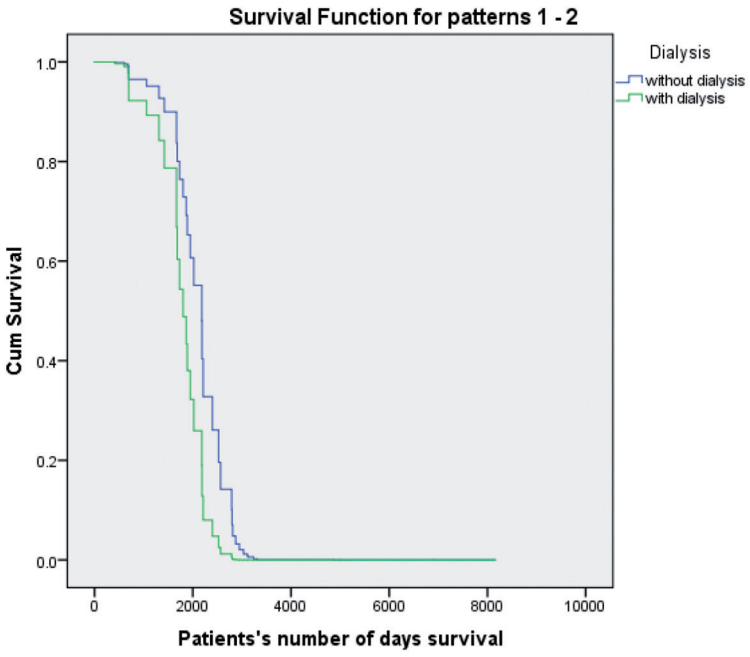

Figure 1. Cox regression survival curve for dialysis and non-dialysis groups. Models: 1 = age at diagnosis, 2 = consanguinity.

test -2 = 205.6 with $p < 10^{-3}$ was statistically significant (Figure 1). The instantaneous proportional risk of death was statistically different between the dialysis and non-dialysis groups. Cox regression analysis showed a correlation between consanguinity and mortality that influenced survival time (B = 2.401, p = 0.000). Patients with consanguineous parents had an 11-fold higher risk of death after advancing age of disease diagnosis (B = –0.079, p = 0.002). Regarding RPGN and the presence of AA amyloidosis **were not statistically significant [■■■ What was not statistically significant?]** with $p < 0.05$ but their confidence interval contains the value "1" **as** FMF is a rare disease **[■■■ Please check changes made here]** and the sample size N = 58 is small, so statistical results are not conclusive; taking colchicine is a preventive factor and it prolongs survival (Table 6).

Discussion

The most important clinical presentation determining the prognosis of FMF is AA amyloidosis, which can occur in 90% of untreated patients around the age of 40 [5, 6]. In our series, non of our patients had ever received colchicine before renal involvement, and the average age of the population was 31.77 ± 12.867 years, this age of 30 was also described in [6], and the mean age of reaching ESRD for our patients was 35 ± 14.47 years, and has been described in the literature as being 33.3 for North Africans patients [6, 7]. Male sex is a poor prognostic factor **as 62.5% of patients [■■■ Are 62.5% of patients male?]** as already described in several publications [8, 9, 10, 11]. Consanguinity is present in half of our patients (50.3%), while it has been described as being 22.6 – 34% in the Algerian population [12, 13]. As for the triggers of renal damage, infectious process was the most frequent factor with 22 (37.9%) of our patients and 17 (85%) in the Turkish population described in [14]. Nephrotic syndrome was the most common sign in our patients 54 (94.7%), but the most frequent risk factors in our series for CKD development are: high proteinuria, high creatinine level, presence of amyloid nephropathy, number of sclerosed glomeruli > 50%, and RPGN as has been reported in the literature in patients with AA renal amyloidosis secondary to FMF [15, 16, 17]. The presence of RPGN has been reported in the literature [18], and high proteinuria second-

Table 6. Impact of several parameters at the beginning of hospitalization on the mortality of our patients using the multivariable Cox regression model adjusted for age at diagnosis and consanguinity.

Parameters	B	Exp(B)	95.0% CI for Exp(B)		p-values α = 0.05
			Lower	Upper	
Gender of patients	–0.419	0.658	0.246	1.760	0.404
Age at first FMF attack	0.104	1.109	0.995	1.236	0.061
Age at diagnosis	**–0.079**	**0.924**	**0.878**	**0.972**	**0.002**
Consanguinity	**2.401**	**11.033**	**3.020**	**40.304**	**0.000**
Family form of FMF	1.054	2.870	0.868	9.488	0.084
Dialysis	–1.104	0.331	0.010	11.093	0.538
HBP	0.585	1.794	0.573	5.617	0.315
RPGN	–4.105	0.016	0.001	0.458	0.015
CRP	0.005	1.005	0.992	1.019	0.416
≥ 2 mutations in *MEFV* gene	0.066	1.069	0.384	2.972	0.899
Presence of AA amyloidosis	–1.768	0.171	0.036	0.798	0.025
Sclerosed glomeruli ≥ 50%.	–0.268	0.765	0.043	13.696	0.856
Creatinine level	0.014	1.014	0.993	1.035	0.187
Albumin level	–0.0127	0.880	0.787	0.985	0.026
Proteinuria/day	–0.0226	0.798	0.662	0.961	0.017
Taking colchicine	–2.983	0.051	0.005	0.527	0.013

HBP = high blood pressure; RPGN = rapidly progressive glomerulonephritis; CRP = C-reactive protein; Exp(B) = hazard ratio. Bold = statistically significant.

ary to an infectious process is a risk factor for dialysis, as described by Kukuy et al. [14]. Other nephropathies associated with FMF have also been described in several articles [1, 19, 20]. In our study, we noted that these patients were more hypertensive and had microscopic hematuria, and our 6 patients without AA amyloidosis (100%) did well under colchicine and angiotensin II receptor antagonists alone without corticosteroids. They have been described in the literature with better prognosis and death rate than patients with AA amyloidosis [21]. With regards to genetic mutations, in our series, the most frequent mutation is M694I in its homozygous and heterozygous form and also the most described mutation in our country [22, 23] and in Egypt [24], compared to the Moroccan and Tunisian population. For homozygous M694V, all these patients are on dialysis and 2 of them died. This mutation has always been described as associated with a high percentage of AA renal amyloidosis and also with a poor prognosis for the following ethnic groups: Turks, Jews, Armenians, and Arabs [6, 25, 26, 27, 28, 29]. However, a high percentage of homozygous or compound heterozygous patients have been observed in dialysis; in contrast, heterozygote patients are more frequently not-dialyzed [20]. Colchicine has truly changed the game in the treatment of FMF since 1972, with a reduction in the incidence of AA amyloidosis from ~ 50% to 8.6% of patients [26, 29]. Colchicine in combination with angiotensin II receptor blockers has been shown to be effective in patients with FMF-associated renal failure [20] and has been shown to be effective in 29 (50%) of our treated patients, regardless of whether they had AA amyloidosis or another kidney disease [30]. Colchicine resistance was reported in 5 (8.6%) of our patients and is present in 10% of treated patients [30].

Conclusion

The results of our study show that our patients had never been diagnosed with FMF before and had never been put on colchicine. The diagnosis was concomitant with the onset of renal involvement. Consanguinity and age at diagnosis are independent risk factors for increased mortality in dialysis patients compared to non-dialysis patients who had a better prognosis on colchicine and antiproteinuric drugs, with systematic screening and family management. AA renal amyloidosis secondary to FMF is the tip of the iceberg; the sample is certainly small because it is a rare disease in nephrology, but our study will

help and guide other clinicians in our country (pediatricians, rheumatologists, internists ...) to be interested in this disease.

Acknowledgment

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Availability of data and materials

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Ethical approval and consent to participate

The study protocol was approved by the Benyoucef Benkhedda Medical University and all participants provided written informed consent.

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Conflict of interest

The authors declare that they have no competing interests.

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