Risk Factors for Amyloidosis and Impact of Kidney Transplantation on the Course of Familial Mediterranean Fever

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ABSTRACT: **Background:** Amyloidosis of familial Mediterranean fever (FMF) may lead to end-stage renal failure, culminating in kidney transplantation in some patients.

Objectives: To assess demographic, clinical and genetic risk factors for the development of FMF amyloidosis in a subset of kidney-transplanted patients and to evaluate the impact of transplantation on the FMF course.

Methods: Demographic, clinical and genetic data were abstracted from the files, interviews and examinations of 16 kidney-transplanted FMF amyloidosis patients and compared with the data of 18 FMF patients without amyloidosis.

Results: Age at disease onset and clinical severity of the FMF amyloidosis patients prior to transplantation were similar to FMF patients without amyloidosis. Compliance with colchicine treatment, however, was much lower (50% vs. 98 %). Post-transplantation, FMF amyloidosis patients experienced fewer of the typical serosal attacks than did their counterparts (mean 2214 days since last attack vs. 143 days). Patients with FMF amyloidosis carried only M694V mutations in the FMF gene, while FMF without amyloidosis featured other mutations as well.

Conclusions: Compliance with treatment and genetic makeup but not severity of FMF constitutes major risk factors for the development of amyloidosis in FMF. Transplantation seems to prevent FMF attacks. The protective role of immunosuppressive therapy cannot be excluded.

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KEY WORDS: familial Mediterranean fever (FMF), genetics, amyloidosis, kidney transplantation, colchicine

Familial Mediterranean fever is a genetic autoinflammatory disease caused by mutations in the FMF gene (*MEFV*) and manifests with recurrent fever and polyserositis. A devastating sequela of FMF is renal amyloidosis, occurring in up to 50%–60% of untreated patients [1]. Renal amyloidosis is evident initially by the presence of proteinuria and nephrotic syndrome and eventually leads to end-stage renal failure. It results from kidney deposition of the AA protein, a cleavage product of the acute-phase reactant SAA [2]. Over the years, several risk factors for the development of amyloidosis among FMF patients have emerged, including a family history of FMF amyloidosis, consanguinity of the patient's parents, M694V homozygosity, ethnicity (higher in Jews of North African origin and Turks, and less common in Arabs), male gender, high SAA levels, isoform α/α of SAA, and country of residence [3,4]. Although the clinical picture, particularly the presence of joint disease, does play a role, it is noteworthy that amyloidosis may develop in patients who never experienced clinically overt FMF (phenotype II).

A turning point in the history of FMF has been the insertion of colchicine into the treatment regimen, which has significantly diminished the incidence of amyloidosis in this population. This was first reported by Zemer et al. [5]. Higher rates of FMF-related amyloidosis are noted in patients with low compliance to colchicine therapy and in patients who initiated colchicine at an older age [6,7]. Continuous colchicine treatment was shown to prevent amyloid re-accumulation in the grafted kidney of FMF patients with amyloidosis [7].

In the present study we evaluated various factors that underline the evolvement of amyloidosis in a subset of FMF patients who underwent kidney transplantation, and assessed how transplantation and immunosuppression affects the clinical picture of FMF.

PATIENTS AND METHODS

In this retrospective analysis we compared demographic, clinical and genetic data of FMF patients with and without amyloidosis. All 16 amyloidosis patients had undergone kidney transplanta-

FMF = familial Mediterranean fever

tion and were recruited from the kidney transplantation clinics at the Rabin Medical Center (Beilinson campus) and Sheba Medical Center. The diagnosis of kidney amyloidosis was determined by kidney biopsy or by typical clinical presentation of renal amyloidosis with amyloid-positive extrarenal biopsy.

The control group consisted of 18 consecutive FMF patients without amyloidosis (as attested by normal urine analysis) or other kidney-related diseases. The control patients were recruited from the clinic of the national FMF center at Sheba Medical Center, Tel Hashomer. In both groups, the Tel Hashomer criteria were used for the diagnosis of FMF [8]. All patients were interviewed and examined and completed a questionnaire detailing clinical, demographic and genetic characteristics. The FMF severity was assessed using the FMF severity scale of Mor and collaborators [9]. *MEFV* mutation analysis was performed in those not tested previously. The study was approved by the ethics committee at Sheba Medical Center. All patients signed an informed consent.

DETECTION OF COMMON *MEFV* MUTATIONS

Genomic DNA was prepared from 200 µl of whole blood, using a commercial kit (high template polymerase chain reaction preparation kit, Roche IL, USA). The three most common *MEFV* mutations – M694V, V726A and E148Q – identifying 70% of the FMF alleles in the Israeli-Jewish FMF patient population were determined, using polymerase chain reaction amplified segments of exon 10 and exon 2 of *MEFV* and enzyme restriction analysis, as previously described [10].

DATA ANALYSIS

Chi-square test was used for categorical variables, and Student's *t*-test for continuous variables. All tests were two-tailed. *P* value < 0.05 was defined as statistically significant.

RESULTS

Male preponderance and older age characterized the kidney-transplanted FMF amyloidosis group [Table 1]. The majority of FMF amyloidosis patients originated from North African Jewish immigrants (mainly from Morocco). The other distinct patient ethnicities in the study group varied insignificantly from those of the control group.

With regard to the pre-transplantation period of the FMF amyloidosis group, the clinical parameters of the two FMF patient groups appeared to be comparable. This included site of attacks, rate of attacks accompanied by fever, duration of attacks, pain score during attacks, prescribed colchicine dose, age at onset, diagnosis delay, and disease severity score [Table 1].

COLCHICINE TREATMENT

Both patient groups were prescribed a mean of 1.5 mg colchicine a day by their treating physicians. However, while patients of the control group reported a 94% compliance rate, the kidney-transplanted FMF amyloidosis patients admitted only a 50% compliance rate in the pre-transplantation period ($P = 0.05$). It is noteworthy that the FMF amyloidosis group reported a near 100% compliance *after* amyloidosis had been diagnosed.

Table 1. Demographic and clinical* parameters of FMF patients with amyloidosis

Clinical data	FMF with amyloidosis	FMF without amyloidosis	*P* value
No. of patients	16	18	–
Males	9 (57%)	6 (33%)	0.05
Mean age (yrs)	49	38	0.025
North African origin	14 (87%)	8 (44%)	0.01
Age at 1st attack (yrs)	13 ± 15	19 ± 15	0.34
Peritonitis	14 (87%)	17 (94%)	0.6
Arthritis	12 (75%)	16 (88%)	0.4
Pleuritis	6 (37%)	10 (55%)	0.3
Duration of attack (hrs)	24–72	24–72	0.9
Pain score VAS (1–10)	7–10	6–10	0.9
Hospitalization during attacks (at least one)	9 (56.25%)	11 (61.1%)	0.8
Abdominal surgery	3 (18.75%)	8 (44.4%)	0.23
Time from disease onset to diagnosis (yrs)	10.5 ± 8.73	7.67 ± 8.42	0.34
Disease severity score (9)	8 ± 1 (moderate)	7 ± 2 (moderate)	0.24

*Clinical parameters relate to the pre-transplantation period

Table 2. *MEFV* mutations in FMF patients with amyloidosis

Genetic mutations	FMF with amyloidosis (n=16)	FMF without amyloidosis (n=18)
M694V/M694V	12	9
M694V/0	2	1
V726A/V726A	0	3
V726A/0	0	2
E148Q/M694V	0	2
Not performed	2	0
No mutations	0	1

GENETICS

MEFV mutations are shown in Table 2. Fourteen of the 16 kidney-transplanted FMF amyloidosis patients underwent genetic analysis, which resulted in the detection of the M694V *MEVF* mutation in all (12 homozygous, and 2 heterozygous). By contrast, among all 18 FMF patients without amyloidosis, only 12 (66%) had any M694V mutation. The rest had V726A/V726A (n=3), V726A/0 (n=2), or no mutations at all (n=1). The difference between the patient and control groups in carriage of

at least one M694V mutation was significant ($P = 0.02$). There was no difference in the rate of homozygosity to the M649V mutation, the main known genetic risk factor for amyloidosis.

POST-TRANSPLANTATION ERA

The number of years since kidney transplantation in the study patients was 6.75 ± 6.75 on average; 81% of them underwent dialysis treatments for 2.37 ± 1.7 years before transplantation. All reported 100% compliance with the prescribed immunosuppressive therapy, which included mycophenolate mofetil along with tacrolimus or cyclosporine, with or without prednisone. Three patients were switched to azathiopurine at some point. Blood levels of tacrolimus and cyclosporine were monitored periodically. While FMF patients without amyloidosis recalled that their most recent FMF attack occurred 143 days (average) before the day they completed the questionnaire, in FMF-amyloidosis patients it occurred 2214 days before the questionnaire ($P = 0.01$).

DISCUSSION

In this small cross-sectional study, we retrospectively studied some factors that may pose a risk for the development of amyloidosis in a subgroup of FMF amyloidosis patients who underwent kidney transplantation. Low compliance to colchicine treatment, homozygosity to M694V mutations, male gender and North African origin (mainly Moroccan) were found to be factors that might relate to the development of amyloidosis in this group. The severity of FMF prior to transplantation appeared not to predict the future occurrence of amyloidosis. Our observation is supported by previous studies on the role of the M694V genotype, colchicine treatment and compliance with treatment [11-13].

Interestingly, in the study by Sevoyan et al [6], with results similar to ours, the severity of FMF in patients who developed amyloidosis was comparable to that of the controls. The occurrence of phenotype II amyloidosis, and the finding that 2 mg/day of colchicine protects against amyloidosis, even if the FMF attacks are not controlled, concur with this finding and confirm that a combination of risk factors rather than one dominant factor underlie, eventually, the development of amyloidosis.

Another finding of interest was that renal transplantation, and/or the adjunct administration of immunosuppressive therapy, seems to prevent FMF attacks in FMF amyloidosis patients. A review of the literature does not shed much light on the usefulness of various immunosuppressive agents such as prednisone, cyclosporine, MMF or azathioprine for the control of FMF attacks, perhaps due to the high success rates of colchicine treatment when administered properly, and the reluctance of physicians to prescribe such unsafe drugs that have serious side effects for life. While prednisone is frequently used for vasculitidis, such as protracted febrile myalgia, which complicates FMF [14], its effect on the suppression of FMF attacks was not adequately determined. One study demonstrated that cyclosporine was superior to azathioprine for post-transplantation immunosuppression in FMF amyloidosis, but their effect on FMF symptoms was not described [15]. Based on a large number of case reports, the efficacy of potent anti-inflammatory medications, such as anti-tumor necrosis factor and anti-interleukin-1 preparations, offer much promise for patients with severe colchicine-refractory FMF [16-18].

Our study has some limitations. One is the small sample size of FMF patients with amyloidosis, which stems from the rarity of this complication today. Another limitation is that the study was retrospective. However, a prospective study is extremely difficult to perform in patients with this disease due to the time lapse from FMF diagnosis to development of amyloidosis, which takes decades and may be significantly affected by various interventions.

MMF = mycophenolate mofetil

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References

1. Pras M, Bronshpigel N, Zemer D, Gafni J. Variable incidence of amyloidosis in familial Mediterranean fever among different ethnic groups. *Johns Hopkins Med J* 1982; 150 (1): 22-6.
2. El-Shanti HI. Familial Mediterranean fever and renal disease. *Saudi J Kidney Dis Transpl* 2003; 14 (3): 378-85.
3. Livneh A. Amyloidosis of familial Mediterranean fever (FMF) – insights to FMF phenotype II. *Harefuah* 2006; 145 (10): 743-5, 82 (Hebrew).
4. Gershoni-Baruch R, Brik R, Zacks N, Shinawi M, Lidar M, Livneh A. The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. *Arthritis Rheum* 2003; 48 (4): 1149-55.
5. Zemer D, Revach M, Pras M, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. *N Engl J Med* 1974; 291 (18): 932-4.
6. Sevoyan MK, Sarkisian TF, Beglaryan AA, Shahsuvaryan GR, Armenian HK. Prevention of amyloidosis in familial Mediterranean fever with colchicine: a case-control study in Armenia. *Med Princ Pract* 2009; 18 (6): 441-6.
7. Livneh A, Zemer D, Siegal B, Laor A, Sohar E, Pras M. Colchicine prevents kidney transplant amyloidosis in familial Mediterranean fever. *Nephron* 1992; 60 (4): 418-22.
8. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40 (10): 1879-85.
9. Mor A, Shinar Y, Zaks N, et al. Evaluation of disease severity in familial Mediterranean fever. *Semin Arthritis Rheum* 2005; 35 (1): 57-64.
10. Kogan A, Shinar Y, Lidar M, et al. Common MEFV mutations among Jewish ethnic groups in Israel: high frequency of carrier and phenotype III states and absence of a perceptible biological advantage for the carrier state. *Am J Med Genet* 2001; 102 (3): 272-6.
11. Livneh A, Langevitz P, Shinar Y, et al. MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. *Amyloid* 1999; 6 (1): 1-6.
12. Zaks N, Shinar Y, Padeh S, et al. Analysis of the three most common MEFV