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Serum Amyloid A Levels in Kidney-Transplanted Patients with Familial Mediterranean Fever-Amyloidosis

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ABSTRACT: **Background:** Amyloidosis of familial Mediterranean fever (FMF) may lead to end-stage renal failure, culminating in kidney transplantation. Since amyloidosis is prompted by high serum amyloid A (SAA) levels, increased SAA is expected to persist after transplantation. However, no data are available to confirm such an assumption.

Objectives: To determine SAA levels in kidney-transplanted FMF-amyloidosis patients and evaluate risk factors for the expected high SAA levels in this patient group.

Methods: SAA, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were obtained from 16 kidney-transplanted FMF-amyloidosis patients, 18 FMF patients without amyloidosis and 20 kidney-transplanted patients with non-inflammatory underlying disease. Demographic, clinical and genetic risk factors evaluation was based on data extracted from files, interviews and examination of the patients.

Results: SAA level in FMF patients who underwent kidney transplantation due to amyloidosis was elevated with a mean of 21.1 ± 11.8 mg/L (normal ≤ 10 mg/L). It was comparable to that of transplanted patients with non-inflammatory disorders, but tended to be higher than in FMF patients without amyloidosis (7.38 ± 6.36, $P = 0.08$). Possible risk factors for the elevated SAA levels in kidney transplant patients that were excluded were ethnic origin, *MEFV* mutations, gender, age and disease duration.

Conclusions: Kidney-transplanted patients with FMF-amyloidosis and with other non-FMF causes displayed mildly elevated SAA levels, possibly resulting from exposure to foreign tissue rather than from various FMF-related factors.

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KEY WORDS: familial Mediterranean fever, amyloidosis, serum amyloid A, kidney transplantation, colchicine

Familial Mediterranean fever is an auto-inflammatory disease characterized by recurrent spontaneous self-limited febrile attacks of peritonitis, pleuritis and arthritis, accompanied by elevation of acute-phase reactants [1]. The majority of patients are asymptomatic between attacks, even when untreated. A devastating consequence of long-lasting FMF, affecting a small but significant proportion of patients, is reactive AA amyloidosis [2]. The amyloidosis of FMF results from tissue deposition of the N-terminal segment of the acute-phase protein serum amyloid A [3]. Proteinuria is most often the first sign of FMF-amyloidosis, which may gradually progress though a nephrotic stage into end-stage renal failure necessitating kidney transplantation or hemodialysis. Prophylactic administration of colchicine diminishes the frequency and severity of FMF attacks and prevents amyloidosis in most patients [4,5]. Indeed, a steep decline in the incidence of FMF-associated amyloidosis has been observed since the widespread use of colchicine for FMF patients [1]. Nevertheless, at the national FMF center located at Sheba Medical Center, Tel Hashomer, up to five new cases of kidney disease are diagnosed annually, mostly due to amyloidosis.

SAA is an acute-phase reactant created during an FMF attack or other inflammatory conditions such as infection, malignancy and tissue injury (e.g., myocardial infarction) [6]. Higher than normal SAA levels may put the patient at risk and are a prerequisite for the development of amyloidosis [2,7]. Therefore, increased SAA is expected to be found in FMF-amyloidosis patients, even after kidney transplantation. However, no data are available to confirm this assumption. Since SAA level is an important factor used to monitor colchicine treatment [8], we aimed to determine SAA levels and other inflammatory markers in FMF patients who underwent kidney transplantation due to amyloidosis as well as evaluate the risk factors for high SAA levels in this patient group.

FMF = familial Mediterranean fever
SAA = serum amyloid A

PATIENTS AND METHODS

In this cross-sectional study SAA, CRP and ESR were obtained from three patient groups comprising 54 male and female patients of Jewish origin. The study group consisted of 16 kidney-transplanted FMF-amyloidosis patients. The diagnosis of amyloidosis was determined by a positive kidney biopsy, or by typical clinical presentation of renal amyloidosis with amyloid-positive extrarenal biopsy. There were two control groups: the control 1 group consisted of 20 kidney-transplanted patients without FMF, infection or other inflammatory diseases who underwent kidney transplantation due to end-stage renal failure caused by diabetes (n=9), hypertension (n=3), immunoglobulin A nephropathy (n=3), adult polycystic kidney disease (n=4), or history of vesicoureteral reflux disease (n=1). The control 2 group comprised 18 FMF patients without amyloidosis (as attested by normal urine analysis) or other kidney-related diseases.

Consecutive FMF patients, including those with a kidney transplant, were recruited from the clinic of the national FMF center at Sheba Medical Center, Tel Hashomer. Kidney transplant patients were also recruited randomly from the kidney transplantation clinics at Rabin Medical Center (Beilinson campus) and Sheba Medical Center. FMF was diagnosed according to an accepted set of criteria [9]. All patients were interviewed and examined; they completed a questionnaire on clinical, demographic and genetic characteristics, and donated blood samples for the study of inflammatory markers. FMF severity score was assessed according to the 2005 criteria of Mor et al. [10]. The study was approved by the institutional review board. All patients signed an informed consent.

SAA, CRP AND ESR DETERMINATION

Blood samples for measuring SAA, CRP and ESR levels were drawn at least 2 weeks after the last FMF attack, only after ruling out the possible presence of an inflammatory or infectious condition. SAA was determined using nephelometry according to the manufacturer's instructions (Dade Behring, Marburg, Germany). CRP was measured using an immune-turbidimetric test with the Olympus analyzer (Olympus Life and Material Science Europe, Hamburg, Germany). ESR was measured by the standard method. Normal SAA levels were considered as ≤ 10 mg/L, normal CRP as ≤ 5 mg/L, and ESR as ≤ 20 mm/hr.

DATA ANALYSIS

Statistical analysis was performed using the chi-square test for categorical variables, and Student's *t*-test for comparison of continuous variables. All tests were two-tailed. *P* values < 0.05 were considered statistically significant. To study risk factors for SAA elevation in kidney-transplanted patients we combined patients of the FMF and the non-FMF groups into one cohort of patients.

CRP – C-reactive protein
ESR = erythrocyte sedimentation rate

Table 1. Demographic parameters

	FMF kidney transplanted	Non-FMF kidney transplanted	FMF
	Study group (n=16)	Control 1 (n=20)	Control 2 (n=18)
Age (yrs) (mean)	49	56	38
Men	9 (57%)	19 (95%)	6 (33%)
Ethnic origin (all Jewish)			
North Africa	14 (87%)	7 (35%)	8 (44%)
Turkey	1 (6%)	0 (0%)	3 (16%)
Iraq	1 (6%)	7 (35%)	3 (16%)
Europe	0	6 (30%)	4 (22%)

Comparison of demographic parameters in 16 kidney-transplanted FMF-amyloidosis patients, 20 kidney-transplanted patients with non-inflammatory underlying disease, and 18 FMF patients without amyloidosis

RESULTS

DEMOGRAPHIC PARAMETERS

Demographic parameters of patients in the three patient groups are detailed in Table 1. The FMF kidney-transplanted patients were significantly older than FMF patients without amyloidosis ($P = 0.025$), but tended to be younger than non-FMF kidney-transplanted patients ($P = 0.17$). Male preponderance characterized the two kidney transplant patient groups. The majority of FMF kidney-transplanted patients were North African immigrants (mainly from Morocco). The other distinct patient ethnicities in the control groups varied insignificantly from those of the study group.

CLINICAL PARAMETERS

All the clinical parameters of FMF patients (transplanted and non-transplanted) appeared to be comparable, without statistically significant differences. This included site of attacks, rate of attacks accompanied by fever, duration of attacks, pain score during attacks, colchicine dose, age at onset, diagnosis delay, and disease severity score (data not shown).

The clinical features of the kidney-transplanted patients in the FMF and the non-FMF groups appeared to be alike in most parameters. These include the proportion of patients undergoing dialysis prior to transplantation, duration of dialysis, living source of kidney transplant, and compliance with the immunosuppressive therapy (prednisone, mycophenolate mofetil and tacrolimus in most patients). The two patient groups differed in the rate of biopsy-proven diagnoses (100% vs. 50%, $P < 0.001$) and status of the transplanted kidney, which was worse in non-FMF patients with respect to proteinuria > 200 mg/day (70% vs. 18%, $P = 0.02$). There was also a trend for a higher rate of patients with serum creatinine > 1.2 mg/dl in this group (30% vs. 18%), and a trend for a longer time period from transplantation (6 ± 6.7 vs. 4 ± 3.3 respectively, $P = 0.07$).

Table 2. Inflammatory markers of study group and two control groups

Inflammatory markers	FMF transplanted	FMF non-transplanted	*P* value	Non-FMF-transplanted	*P* value
ESR (mm/hr)	14 ± 1.5	17 ± 2.6	0.3	8 ± 2.5	0.07
CRP (mg/L)	13 ± 11.6	4 ± 1.2	0.004	6 ± 6.4	0.02
SAA (mg/L)	21 ± 11	7 ± 6.3	0.08	21 ± 20.1	0.9

P values are for comparisons of the study group (FMF transplanted patients) with the control groups. Normal SAA levels were considered as ≤ 10 mg/L, normal CRP as ≤ 5 mg/L, and ESR as ≤ 20 mm/hr

INFLAMMATORY MARKERS

The inflammatory markers of kidney-transplanted FMF patients compared to the two control groups are shown in Table 2. While all parameters appeared to be normal in non-transplanted FMF patients, SAA levels in the two kidney-transplanted groups were comparable but slightly above normal. Of note, CRP levels in transplanted FMF patients were elevated and significantly above the normal levels of non-transplanted FMF patients and above the slightly elevated levels of non-FMF transplanted patients.

CLINICAL AND DEMOGRAPHIC CORRELATES OF HIGH SAA LEVELS

In light of the similar SAA levels in both the FMF and the non-FMF transplanted groups, we combined the two groups into one to study risk factors underlying the elevated SAA levels found in kidney-transplanted patients. Patient age (above or below 50 years), gender, ethnic origin, the source of the kidney (living vs. cadaveric), previous hemodialysis, creatinine levels above 1.2 mg/dl, degree of proteinuria, time after transplantation, FMF severity score and FMF genotype (M694V homogenous vs. other genotypes) did not correlate with SAA levels (data not shown). Similar analysis for CRP levels also failed to demonstrate a correlation between CRP levels and the studied parameters.

DISCUSSION

We found that FMF patients who underwent kidney transplantation had a moderate elevation of SAA (21 mg/L) and CRP (13.9 mg/L) levels, compared to those without kidney transplantation in whom inflammatory markers, on average, were not elevated [Table 2]. In the group of kidney transplantation unrelated to FMF or other inflammatory conditions, SAA levels were also elevated (21 mg/L), yet CRP was near normal. These results suggest that SAA levels are mildly elevated in all kidney-transplanted patients regardless of having FMF. We were not able to identify clinical, genetic or demographic risk factors for elevated SAA or CRP levels in all the transplanted patients, and we therefore speculate that organ transplantation itself results in subclinical inflammation, perhaps due to the patient's reaction to a foreign body.

Another finding was that FMF patients who underwent kidney transplantation had a better post-transplantation kidney condition, defined as serum creatinine < 1.2 mg/dl (not significant trend), or proteinuria ($P < 0.02$) as compared to non-FMF related kidney-transplanted patients. This finding is even more robust if one accounts for the time interval from kidney transplantation, which was shorter in the non-FMF patients. This finding parallels reports by others [11] and suggests that either recurrence of the primary disease to the transplanted kidney is less common in FMF, or colchicine treatment has an added effect in preventing chronic rejection, beyond preventing amyloidosis in the FMF-kidney transplant group.

According to the present study, SAA levels appear to be more sensitive for the detection of inflammation than CRP levels in the non-FMF group. Previous studies by us [8] and others [11] suggest SAA superiority over CRP levels in FMF as well. Since in FMF the determination of SAA levels has an extra benefit of being directly relevant to amyloidosis, SAA testing is preferred for follow-up of FMF subclinical activity in patients with or without kidney damage. The added advantage and the message coming from our work is that the target SAA level for colchicine treatment monitoring in FMF kidney-transplanted patients should be ≤ 20 and not ≤ 10 mg/L.

The use of SAA has become common in patients with organ transplantation, and a correlation of high SAA levels and rejection was demonstrated by others [12,13]. The contribution of the present work to this aspect of SAA testing is that mildly elevated SAA levels found in the post-transplantation stage may not imply rejection as they are not associated with the degree or presence of kidney damage found in these patients, but mildly elevated SAA levels is the rule in all kidney-transplanted patients. We conclude that mild SAA elevation might be expected in kidney-transplanted individuals, probably reflecting the inflammation associated with foreign body reaction. This finding should be accounted for in the treatment of FMF.

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