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In familial Mediterranean fever, soluble TREM-1 plasma level is higher in case of amyloidosis

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Abstract

We aimed to explore triggering receptor expressed on myeloid cells-1 (TREM-1) activation in familial Mediterranean fever (FMF), the most frequent monogenic auto-inflammatory disease, through the measurement of its serum soluble form, named sTREM-1. Blood samples from patients with FMF according to Livneh criteria followed in the French FMF national center and carrying two pathogenic *MEFV* mutations were collected. Serum level of sTREM-1 was assessed using ELISA. Demographic data, presence of FMF attack, association with histologically proven AA amyloidosis, and blood levels of C-reactive protein (CRP), serum amyloid A (SAA) protein, and creatinine were collected. TREM-1 was available in 56 patients (33.9% male, mean age 43 yr); AA amyloidosis was associated in six patients (19.6% in FMF). Mean sTREM-1 level did not differ significantly between patients having an attack or not and there was also no significant correlation between the level of sTREM-1 and CRP and SAA protein. However, the mean rate of sTREM-1 was significantly higher among FMF patients with AA amyloidosis versus without, though the concomitant SAA protein level was normal. Serum level of sTREM-1 was higher in patients with amyloidosis even though the concomitant SAA protein level was normal. sTREM-1 plasma levels could be an accurate tool to specifically identify FMF patients with amyloidosis.

Keywords

TREM-1, familial Mediterranean fever, amyloidosis, disease activity, biomarkers

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Introduction

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a cell surface receptor mainly expressed in monocytes and neutrophils, involved in innate immune responses.[1] TREM-1 acts as an amplifier of the inflammatory response, promoting the production of pro-inflammatory cytokines and chemokines as well as neutrophil degranulation. Following engagement, TREM-1 is shed and releases in the milieu. The role of TREM-1 is well documented in septic conditions,[2] but its role has been poorly studied in auto-inflammatory diseases. We aimed to explore TREM-1 activation in familial Mediterranean fever (FMF), the most frequent monogenic auto-inflammatory disease,

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through the measurement of its serum soluble form, named sTREM-1.

Material and methods

Patients with FMF seen in the French FMF national center between June 2018 and December 2018 in the context of usual care were eligible. FMF was defined clinically according to Livneh criteria and genetically by the carrying of two non-ambiguous pathogenic *MEFV* mutations (homozygous or heterozygous compound) among variants M680I, M694V, M694I, V726A, I692del, K695R, and R761H.[3,4] Blood samples were collected consecutively.

Serum level of sTREM-1 was assessed using ELISA (Quantikine kit, R&D Systems, Lille, France). Demographic data, presence of FMF attack at the time of the blood sample, association with histologically proven AA amyloidosis, and blood levels of C-reactive protein (CRP) (normal value < 5 mg/l), serum amyloid A (SAA) protein (normal value < 6 mg/l), and creatinine were collected.

Results

The main features of FMF patients are reported in Table 1. Of 56 patients, 33.9% were male with a mean age of 43 yr; 87.5% carried one homozygous *MEFV* mutation and 12.5% displayed two *MEFV* mutations; six patients had FMF-associated AA amyloidosis: 4/6 (66.7%) of them were female and all carried M694V homozygous mutation of the *MEFV* gene. Concerning treatments, 95.6% patients were treated with colchicine with a mean dose of 1.5 mg daily, 5/45 (11.1%) patients received anti-IL-1 therapy, among them three with AA amyloidosis; one patient with amyloidosis was concomitantly treated with prednisone 3 mg daily. 19.6% of the samples were collected during an FMF attack; 51.8% had CRP level >5 mg/l and 50% had SAA level >6 mg/l. AA amyloidosis patients were collected during FMF remission.

sTREM-1 was detectable in all patients with a mean level (SD) of 367.3 (198.0) pg/ml. Serum level of sTREM-1 was higher in men than in women (457.8 (266.4) versus 320.9 (1433.7) pg/ml, $P = 0.049$), and was positively correlated with age ($R = 0.65$, $P < 10^{-4}$).

The level of sTREM-1 did not significantly differ between patients having an attack or not (381.0 (125.8) versus 367.3 (214.2) pg/ml, respectively ($P = 0.37$)). In addition, there was no significant correlation between the level of sTREM-1 and CRP ($R = 0.15$) or SAA protein ($R = 0.12$) (both $P > 0.05$). However, the level of sTREM-1 was significantly higher among FMF patients with AA amyloidosis as compared to FMF patients without (639.0 (331.8) versus 334.7 (151.5) pg/ml, $P < 0.01$, Figure 1) Patients with AA amyloidosis having significantly higher creatininemia than FMF patients without amyloidosis (Table 1) and sTREM-1 level being positively correlated with creatininemia ($R = 0.27$, $P = 0.045$), we performed a multivariate regression to determine whether sTREM-1 level remained significantly higher in patients with AA amyloidosis. The difference remained significant after adjusting for creatininemia and gender ($\beta = 0.44$ [0.06–0.83], $P = 0.02$) but not when age was entered in the model ($P = 0.25$). In the complete model, age and creatininemia remained independently associated with sTREM-1 levels ($P = 0.03$ and $P = 0.01$, respectively).

Table 1. Characteristics of 56 patients with familial Mediterranean fever included in this study.

	All ($n = 56$)	FMF with amyloidosis ($n = 6$)	FMF without amyloidosis ($n = 50$)	*P*-value
Male, *n* (%)	19 (33.9%)	2 (33.3%)	17 (34.0%)	1
Mean age, yr (SD)	43.0 (16.9)	60.2 (16.3)	40.9 (11.2)	$<10^{-4}$
Homozygous *MEFV* mutation, *n* (%)	49 (87.5%)	6 (100.0%)	41 (82.0%)	1
FMF attacks during the study, *n* (%)	11 (19.6%)	0 (0.0%)	11 (22.0%)	0.33
Colchicine intake, *n* (%)	43/45 (95.6)	4/5 (80.0)	39/40 (97.5)	0.52
Dosage of colchicine (mg/d), mean (SD)	1.5 (0.6)	1.4 (0.9)	1.6 (0.6)	0.57
Oral corticosteroids or prednisone intake, *n* (%)	1/45 (2.2)	0 (0.0)	1/40 (2.5)	1
Anti-IL-1 therapy, *n* (%)	5/45 (11.1)	3/5 (60.0)	2/40 (5.0)	<0.01
Serum sTREM-1 level (pg/ml), mean (SD)	367.3 (198.0)	639.0 (331.8)	334.7 (150.5)	<0.01
Serum creatinine level (μmol/l), mean (SD)	76.9 (78.8)	131.5 (67.4)	71.4 (77.4)	<0.01
C-reactive protein (mg/l), mean (SD)	16.0 (24.6)	2.8 (2.0)	17.6 (25.6)	<0.05
Serum A amyloid (>6 mg/l), mean (SD)	24.7 (53.3)	0 (0.0)	27.8 (55.8)	<0.05

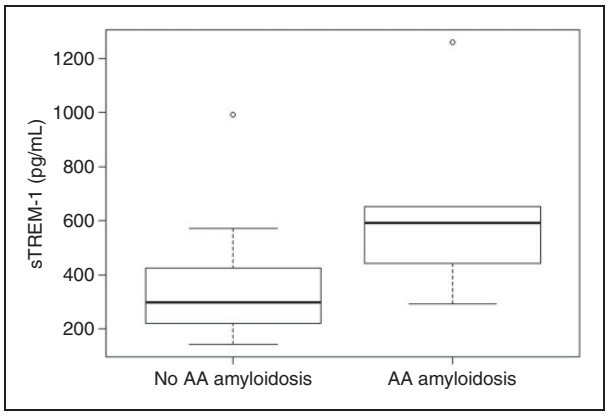

Figure 1. Serum level of sTREM-1 in 56 patients with familial Mediterranean fever according to AA amyloidosis status sTREM-1 was detectable in all patients. The mean rate (SD) of sTREM-1 was significantly higher among FMF patients with AA amyloidosis versus without: 639.0 (331.8) pg/ml versus 334.7 (151.5) pg/ml, respectively.
sTREM-1: soluble Triggering Receptor Expressed on Myeloid cells-1

Discussion

In this study, we explored for the first time TREM-1 activation in a monogenic auto-inflammatory disease: FMF, through the measurement of its plasma soluble form. Mean sTREM-1 level was neither correlated with FMF attacks nor with biomarkers of disease activity. These results are unexpected given the involvement of the innate immune response in auto-inflammatory diseases. It would be interesting to investigate how the sTREM-1 level is dynamic after treatment as a complementary approach in further studies. Interestingly, we found that sTREM-1 level was higher in FMF patients with AA amyloidosis, whereas levels of CRP and SAA proteins were similar or significantly lower. As age, amyloid phenotype and creatinine level are strongly correlated with disease severity statistical power is too low to exclude a relationship between sTREM-1 level and amyloidosis in the multivariable regression model. Higher sTREM-1 level in amyloidosis could be related to both macrophage and neutrophil activation responsible for recurrent inflammation in FMF, eventually leading to AA amyloidosis.[5] Macrophages are often detected close to amyloid deposits and are significantly involved in plaque formation and degradation, independently of amyloid protein.[6] Amyloid fibrils can promote neutrophils to secrete pro-inflammatory cytokines such as IL-1β and TNF-α and thus induce liver SAA protein production.[7,8] In addition, some neutrophil-specific proteins such as elastase and histones have been described in amyloid proteins, suggesting a role of neutrophils in deposit formation.[9] The mechanisms that drive TREM-1 activation remains poorly known but we can speculate that amyloid protein directly activates this receptor within inflamed tissues.

Our study has limitations. There is an unusual female predominance in our study. Studies on gender differences in FMF are scarce. A survey of 470 cases reported a 3:2 male:female ratio although the disease is equally prevalent in children of both sexes.[10,11] This unbalanced ratio is unexplained by the autosomal recessive inheritance of FMF and might be explained by a non-homogeneous recruitment into our cohort.

Finally, we did not include control groups. It would have been interesting to compare the sTREM-1 level in control subjects.

In conclusion, in a French cohort of 56 patients with FMF, serum level of sTREM was not associated with disease activity features. However, serum level of sTREM-1 was higher in patients with amyloidosis even though the concomitant SAA protein level was normal. Further studies are needed to clarify the TREM-1 pathway activation in amyloidosis. It could be interesting in the future to evaluate whether sTREM-1 plasma level could be an accurate tool to specifically identify FMF patients with amyloidosis.

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