

# Familial Mediterranean fever (FMF)-associated amyloidosis in childhood. Clinical features, course and outcome

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## Abstract

### Objective

*Familial Mediterranean fever (FMF) is an autosomal recessive disorder of childhood characterized by attacks of fever and serositis. Renal amyloidosis is the most important complication of the disease that determines the prognosis.*

### Methods

*Forty-eight Turkish FMF patients with amyloidosis who have been followed at the two hospitals in Ankara were included in this study.*

### Results

*All patients with amyloidosis had been symptomatic for FMF at the time of the diagnosis (Phenotype I), none had received regular colchicine therapy and all presented with proteinuria. Ten of them had asymptomatic proteinuria; 38 had nephrotic syndrome and 8 of them had renal insufficiency (CRI) as well, at the time of the diagnosis. Regular colchicine therapy was commenced to all of the patients. At the end of observation period of  $4.5 \pm 2.23$  years (range 2-12 yrs) on treatment, nephrotic syndrome resolved in 13 patients and proteinuria was lost in 5 of them. None but 2 of the patients who were diagnosed at proteinuric stage progressed to end stage renal failure (ESRF). Seven MEFV mutations (M694V, M680I, V726A, M694I, K695R, R761H, E148Q) were systematically investigated in 32 patients. Six of the seven studied mutations were found in these patients and clinical diagnosis was confirmed by mutation analysis in 24 patients. Eight patients were found to have mutations on one of the alleles.*

### Conclusion

*Amyloidosis is the most serious complication of FMF. Colchicine treatment ameliorates the progression of renal disease in the patients who presented with proteinuria and even with nephrotic syndrome. No correlation between the outcome of the patients with nephrotic syndrome and the degree of proteinuria and/or serum albumin levels at the initiation of treatment were noted. Progression to ESRF seems inevitable despite colchicine therapy after the development of CRI in patients with FMF associated amyloidosis.*

### Key words

Familial Mediterranean fever, amyloidosis, FMF mutations, colchicine.

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## Introduction

Familial Mediterranean fever is an autosomal recessively inherited disorder. It is characterized by recurrent episodes of fever and inflammation of the peritoneum, pleura, synovial membranes, and skin. The most serious complication of the disease is the development of AA type amyloidosis, it was first diagnosed by Mamou and Cattani in 1952 (1). The typical manifestation of amyloidosis in a formerly known FMF patient is proteinuria, progressing to nephrotic syndrome and uremia, due to the deposition of amyloid fibrils in the kidneys (2). Prolonged colchicine treatment for FMF was introduced in 1972 (3). This regimen prevents or ameliorates the febrile attacks in most of the patients and arrests the development of amyloidosis in all (4, 5). The incidence of amyloidosis in FMF patients has decreased sharply since the introduction of this treatment (6, 7).

The phenotypic features of the disease and the frequency of amyloidosis differs among various ethnic groups and it was emphasized by several authors that Turks have more severe disease with a higher incidence of amyloidosis (8, 9). The gene associated with FMF was cloned in 1997 and several mutations were described since then (10, 11).

The aim of this study was to determine clinical features, course and outcome of Turkish FMF patients who suffer from amyloidosis some of whom had the molecular diagnosis.

## Patients and methods

Forty-eight Turkish FMF patients with amyloidosis who have been followed in the Departments of Pediatric Nephrology of Ankara University Medical School and Ankara Social Security Children's Hospital were included in this study. The diagnosis of FMF and the severity score of the disease (manifested by an earlier age of onset, an increase in the frequency and severity of arthritis, a higher incidence of erysipelas-like erythema, and a higher dose of colchicine to control symptoms) were established according to the previously described criteria (12, 13). As all of the patients had amyloidosis, occurrence of amyloidosis was not considered as a

component of disease severity. All patients who were included in this study presented with persistent proteinuria or nephrotic syndrome at the beginning of the study. The diagnosis was confirmed by the presence of amyloid depositions in the biopsy specimens of the involved tissues in all but one patient. The only patient without renal biopsy had typical FMF symptoms in addition to nephrotic syndrome and a biopsy proven sibling. Kidney tissues were obtained by percutaneous biopsy with the Vim-Silverman or true-cut biopsy needle in 47 cases. Rectum and thyroid biopsies were performed in 14 and 4 patients, respectively. The presence of amyloid deposition was assessed histopathologically by the presence of red metachromasia with gentian violet or green birefringence on polarization microscopy with congo red. All patients were followed prospectively on colchicine therapy by one of the authors during the study period.

Thirty-two patients with amyloidosis were systematically investigated for seven MEFV mutations (M694V, M680I, V726A, M694I, K695R, R761H, E148Q). DNA was extracted from peripheral blood lymphocytes according to standard procedures. Mutation identification was performed according to the previously described PCR and restriction enzyme digestion or amplification refractory mutation system techniques (10, 11, 14-16).

The results were reported as mean  $\pm$  SD.

## Results

Demographic and clinical features of the patients with amyloidosis are shown in Table I. All patients with amyloidosis were symptomatic for FMF at the time of diagnosis (Phenotype I). However, only two of them were diagnosed as FMF and started colchicine treatment before the development of amyloidosis, both were non-compliant to the treatment. The duration between the onset of FMF attacks and the time at diagnosis ranged between 1 and 19 years with a mean of  $6.43 \pm 5.81$  years. Three patients with amyloidosis were noted to have prolonged duration of monoarthritis

**Table I.** Phenotypic features of the patients.

	Amyloidosis	
	n = 48	%
Male/Female	27/21	1.28
Age of onset(years)	7.06 ± 3.38	(1-15 yrs.)
Age at diagnosis(years)	13.03 ± 5.28	(7-26 yrs.)
Fever	41	85%
Abdominal pain	42	88%
Chest pain	18	37%
Arthritis	31	65%
Erysipelas-like erythema	9	18%
Vasculitis	6	13%
Disease severity score	7.30 ± 2.38	(4-11)
Family history of FMF	32	66%
Family history of amyloidosis	27	57%

that can be described as protracted arthritis as the sole manifestation of FMF. The diagnosis of juvenile rheumatoid arthritis and tuberculous arthritis were established in two and one of them, respectively. Synovectomy was carried out in all three and revealed nonspecific synovitis without granuloma formation. The diagnosis of tuberculous arthritis was based on ARB positivity in synovial fluid but specific cultures were negative for mycobacterium tuberculosis. Rheumatoid factor, ANA, and HLA B27 were found negative in all of them. None of them had bone destruction. The diagnosis of FMF could only be established when the history of other clinical manifestations (recurrent abdominal pain, fever, erysipelas-like erythema) be learned. Family history of FMF and amyloidosis were positive in all of these three patients and mutation analysis were support the diagnosis of FMF (M694V/M694V, M694V/ V726A, M680I/

M680I).

Hematuria was detected in three patients with amyloidosis during the follow up examinations on colchicine therapy. Two of them had microscopic hematuria. The third patient with macroscopic hematuria had typical clinical and laboratory features of acute post-streptococcal glomerulonephritis.

All fourteen patients with rectal biopsies were found to have amyloid depositions, while only some of them had gastrointestinal complaints such as transient diarrhea and none of them had intestinal malabsorption. Intractable diarrhea was observed in one patient due to tuberculous peritonitis which resolved after the specific therapy. Eight anemic patients were investigated for duodenal Fe<sup>++</sup> absorption, all were normal. Thyroid glands were found to be enlarged in 32 of 48 patients. All of them were found to be euthyroid on the basis of normal peripheral T4 and TSH levels. Thyroid biopsies were per-

formed in 4 patients, one of which was positive for amyloid depositions.

Table II summarises the renal findings of the patients at presentation and outcome. Regular colchicine therapy (2 mg/d) was commenced to the patients at the beginning of the study and they were followed 4.51 ± 2.23 years (2-12 years) on treatment. At presentation, all of them had persistent proteinuria. Ten had significant proteinuria but not in the nephrotic range (0.5-2 g/24 hours). Main complaints of these patients were fever and acute abdominal pain. Two of them had protracted arthritis in addition to these complaints. Two of the 10 patients who were noncompliant to the treatment, progressed to nephrotic syndrome and renal failure. Proteinuria disappeared in the other 2 patients on regular colchicine treatment. In the remaining 6 patients proteinuria continued in a significant but not in nephrotic range, during the follow-up period. Thirty-eight patients had nephrotic syndrome including 8 with chronic renal insufficiency (CRI) (serum creatinin > 1.5 mg/dL) at the time of the diagnosis. Nephrotic syndrome resolved in 13 patients and proteinuria disappeared in 5 of them within a mean of 2.01 ± 1.04 years ranging between 0.5-4 years. Nephrotic proteinuria ranged between 2 to 10 g/24 hours (4.99 ± 2.73g/24 hour). Serum albumin levels of the patients whose proteinuria disappeared eventually were in the range of 1.1 to 2.3 g/dL within a mean of 1.86 ± 0.45 g/dL at the time of the diagnosis. At the end of the observation period serum albumin levels were found to be 3.0 g/dL and 3.9 g/dL with a mean of 3.45 ± 0.38 g/dL. The degree of proteinuria and serum albumin levels of the 17 patients whose nephrotic syndrome did not resolve were 2-11 g/24 hour (5.48 ± 3.34 g/24hour) and 1-2.5 g/dL (1.76 ± 0.52 g/dL), respectively at presentation. No correlation between the outcome of the patients with nephrotic syndrome and the degree of proteinuria and/or serum albumin levels at the initiation of treatment were noted. Nine patients with nephrotic syndrome and all patients, presented with NS+CRI progressed to ESRF on regular colchicine therapy. Eleven of the 48 patients

**Table II.** Clinical features and outcome of the patients.

At presentation (n = 10)	Outcome (n = 48)			At presentation (n = 38)
PROTEINURIA (n = 10)	2	Normal urine (n = 7)	5	NEPHROTIC SYNDROME (n = 30)
	6	Proteinuria (n = 14)	8	
		NS (n = 8)	8	
	2	ESRF (n = 19)	9	NS + CRI (n = 8)
			8	

NS: Nephrotic syndrome; CRI: chronic renal insufficiency; ESRF: end stage renal failure.

died with renal failure during the follow up period (range 2-12 years).

The seven MEFV mutations (M694V, M680I, V726A, M694I, K695R, R761H, E148Q) were investigated in 32 FMF related amyloidotic patients. Eight of the 32 patients with amyloidosis were homozygotes (3 patients were homozygous for M680I and 5 homozygous for M694V). Fifteen patients were compound heterozygotes for two of the studied mutations. (M694V/V726A in 8, V726A/E148Q in 2, M694V/M680I in 2, M680I/V726A in 1, M694V/M694I in 1 and M680I/M694I in 1) and one patient had a complex allele with M680I/V726A-E148Q mutations. In 8 patients only a single mutation was determined (694V/- in 6, M694I/- in 2). The phenotype-genotype correlation and comparison some of these 32 patients with a group of FMF patients who did not develop amyloidosis were published before (17, 18).

### Discussion

Development of amyloidosis is the most dangerous manifestation of FMF and results from the deposition of amyloid A protein. But, amyloid fibrils have also been reported to infiltrate the adrenals, gastrointestinal tract, liver, spleen, thyroid, lung and at a later stage heart. Renal failure is the most common cause of death and there is generally little dysfunction of the other organs (19, 20).

The appearance of proteinuria is usually the first clinical sign of renal amyloidosis. Persistent proteinuria in an FMF patient, unless proven otherwise, is regarded as evidence of amyloidosis in most of the centers (21). However, non-amyloid glomerular lesions have been described in the patients with FMF (22-24).

Nephropathic amyloidosis is characterized by 4 consecutive stages: preclinical, proteinuric, nephrotic and uremic. The onset and duration of the preclinical stage can not be known. It was reported that amyloidosis developed from 2 months to 14 years after the onset of periodic attacks and the natural duration of amyloidotic kidney disease from the appearance of proteinuria until terminal renal failure ranges be-

tween 2 and 13 years (21). In this study, the overall duration of clinically evident renal amyloidosis, from the diagnosis of proteinuria until renal failure, was found as 4 years, in our two non-compliant patients.

Regular long term treatment with colchicine was reported to prevent amyloidosis and reduce kidney damage in patients with proteinuria, even in the nephrotic stage (4-6, 25). Minimal daily dose required for prevention of amyloidosis is 1 mg. However, patients with amyloidosis are advised to maintain a daily dose of 2 mg in order to decelerate the deterioration of the kidney disease and even to achieve reversal of the proteinuric or the nephrotic stage (26, 27). In our study, none but two non-compliant patients who were diagnosed with significant proteinuria progressed to ESRF at the end of the follow up period on regular colchicine therapy. Moreover nephrotic syndrome resolved in more than one-third of the patients who presented with nephrotic syndrome and proteinuria disappeared in about 40% of them. However, all of the patients with nephrotic syndrome and CRI progressed to ESRF despite regular therapy.

In conclusion, in this study definite ameliorating effect of colchicine in the patients with amyloidosis who were diagnosed with proteinuria and even nephrotic syndrome were observed. No correlation between the outcome of the patients with nephrotic syndrome and the degree of proteinuria and/or serum albumin levels at the initiation of treatment were noted. Progression to ESRF seems inevitable despite colchicine therapy after the development of CRI in the patients with FMF associated amyloidosis.

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