Eur J Pediatr (1997) 156: 619–623

Ü. Saatçi · S. Ozen · S. Özdemir · A. Bakkaloglu
N. Besbas · R. Topaloglu · S. Arslan

Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis

Received: 10 July 1996 and in revised form: 9 December 1996 / Accepted: 10 December 1996

Abstract Familial Mediterranean fever (FMF) is a genetically transmitted disease characterized by recurrent attacks of fever and serositis. The most important complication of this disease is the development of amyloidosis. We present our analysis of 425 FMF patients without and 180 with amyloidosis (123 FMF having amyloidosis type I and 57 FMF having amyloidosis type II). The male/female ratio was higher in the amyloidosis population (111/69) when compared to the FMF population (225/200) ($P = 0.048$). Consanguinity rate was the same among FMF and amyloidosis groups. However, a family history of amyloidosis was significantly more frequent in the amyloidosis group ($P = 0.00001$). Multivariate analysis has revealed that in FMF patients, the presence of a family history of amyloidosis plus consanguinity has a 6.04 fold increased risk of amyloidosis ($P < 0.0001$). The 5-year chronic renal failure free survival was 43.1% and 18.7% in type I and type II amyloidosis, respectively. The time interval to develop chronic renal failure after the development of amyloidosis was 4.8 in type I and 3.0 years in type II, respectively. We found ten cases of Henoch-Schönlein Purpura and nine of polyarteritis nodosa among our patients. The significance of the association between FMF and vasculitis awaits to be clarified. Among the FMF patients put on colchicine therapy (435), only 10 (2.3%) have developed amyloidosis confirming that this drug protects from amyloidosis.

Conclusion Since the presence of a familial history of amyloidosis has been defined as the most important risk factor in the development of amyloidosis, we suggest that additional genetic factors may be operative in the development of amyloidosis.

Ü. Saatçi (✉) · S. Ozen · S. Özdemir · A. Bakkaloglu · N. Besbas
R. Topaloglu · S. Arslan
Hacettepe University Medical Faculty, Department
of Paediatric Nephrology and Rheumatology, TR-06100,
Sihhiye, Ankara, Turkey

Key words Familial Mediterranean fever · Childhood · Amyloidosis · Prognosis

Abbrevations *FMF* Familial Mediterranean fever

Introduction

Familial Mediterranean fever (FMF) was not recognized as a separate disease until 1945. The most striking feature of FMF is that it characteristically affects certain ethnic groups mainly Arabs, Sepharedic Jews, Armenians and Turks. The disease has become more widespread because of migration. FMF is characterized by recurrent self-limited episodes of fever accompanied by peritonitis, pleuritis or sinovitis. Recessive and apparently dominant inheritance of FMF have been shown in the Armenian population [12]. Vertical transmission in the Armenian population is suggested to be due to a high FMF gene frequency estimated as 8% and consequent homozygote/heterozygote marriage leading to pseudodominant inheritance.

The most severe complication of the disease is amyloidosis leading to chronic renal failure. Another severe complication is chronic destructive arthritis resulting in permanent organic damage to the involved joint. In 1972, colchicine was shown to be effective in preventing or ameliorating the attacks [4], and more importantly, it may also improve the prognosis of amyloidosis nephropathy of FMF.

In this retrospective study we evaluated the clinical features, course, complications, prognostic factors of FMF, and the relationship between FMF and amyloidosis.

Patients and methods

In this study, 425 Turkish children with FMF and 180 children with amyloidosis diagnosed over a period of 20 years were included. FMF diagnosis was based on the criteria of Heller et al. [5]. In 5.3% ($n = 47$) of the patients a history of abdominal pain or

fever was lacking. In 35 of these, diagnosis was based on elevated acute phase reactants with periodic serositis and response to colchicine and in 12 it was based on elevated acute phase reactants, periodic serositis, response to colchicine and a family history.

Amyloidosis was diagnosed by renal biopsy in 175 patients and rectal biopsy in 5 patients. Type I amyloidosis was defined as amyloidosis developing subsequent to clinical features of FMF, whereas type II was defined as development of amyloidosis as the initial manifestation.

Statistics

Student's *t*-test for independent samples and one-way analysis of variance (with Tukey's HSD test for post hoc pairwise comparisons) were performed for comparison of group means of continuous variables. Group proportions were compared with the χ^2-test. Median values for time-to-amyloid and time-to-chronic renal failure data were calculated with life table analysis. Univariate survival curve comparisons were performed with log-rank test. Then Cox proportional hazard model was used to adjust the intercorrelations between clinically and/or statistically significant (justified by log-rank test) explanatory variables [1, 11]. Odds ratios were also calculated with Cox proportional hazard model. Statistical significance was assigned to P values lower than 0.05. Statistical Package for Social Sciences (SPSS) for Windows v5.01 was used for all calculations.

Results

We present the results of our 20 years registry as a main referral centre in the country.

The male/female ratio was higher in the amyloidosis population (111/69) when compared to the FMF patients without amyloidosis (225/200) ($P = 0.048$). The mean age of onset in the FMF and amyloidosis groups were 5.5 ± 3.4 and 6.8 ± 3.8, respectively, whereas age of diagnosis were 9.3 ± 3.7 and 11.4 ± 3.4, respectively.

Clinical and laboratory findings of the patients are summarized in Table 1 and 2. Among the FMF patients without amyloidosis and FMF cases having amyloidosis type I, 164 (38.6%) and 58 (47.2%), respectively complained of arthralgia whereas 73 (17.2%) and 42 (34.1%), respectively, had arthritis. In 78.4% of these cases less than three joints were involved. The joint localizations were upper extremities in 46 (29%), lower extremities in 137 (88.4%), and hip in 11 (7.1%).

A number of systemic diseases have been associated with FMF alone or with FMF and amyloidosis (Table 3).

In 4 of the FMF patients renal biopsy failed to show amyloidosis and 1 membranoproliferative glomerulonephritis, 1 minimal change disease and 2 focal glomerulosclerosis were diagnosed.

Consanguinity rate was the same in both FMF and amyloidosis groups. However, a family history of amyloidosis was significantly more frequent in the amyloidosis group (27.4%) when compared to FMF patients without amyloidosis (7.9%) ($P = 0.00001$).

Multivariate analysis revealed that the presence of a family history of amyloidosis plus consanguinity has a

Table 1 Clinical findings of the patients

	FMF without amyloidosis ($n = 425$) Number (%)	FMF having amyloidosis type 1 ($n = 123$) Number (%)	*P*
Fever	378 (88.9)	66 (53.7)	0.00001
Abdominal pain	406 (95.5)	85 (69.1)	0.00001
Chest pain	66 (15.5)	8 (6.5)	0.015
Arthralgia	164 (38.6)	58 (47.2)	0.11
Arthritis	73 (17.2)	42 (34.1)	0.00008
Hip pain	9 (2.1)	3 (2.4)	0.74

Table 2 The main clinical and laboratory findings of the patients

	Total ($n = 605$) Number (%)	FMF without amyloidosis ($n = 425$) Number (%)	FMF having amyloidosis type 1 ($n = 123$) Number (%)	FMF having amyloidosis type 2 ($n = 57$) Number (%)	*P*
Hepatomegaly	86 (14.2)	37 (8.7)	34 (27.6)	15 (26.3)	0.00001[a]
Splenomegaly	51 (8.4)	31 (7.3)	14 (11.4)	6 (10.5)	0.30
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Hb (g/dl)	11.8 ± 1.8	12.0 ± 1.5	11.2 ± 2.1	11.4 ± 2.4	0.0001[b]
WBC (/mm^3)	10700 ± 5400	10100 ± 4800	11400 ± 56200	13300 ± 8200	0.0001[c]
ESR (mm/h)	58 ± 36	50 ± 32	88 ± 37	93 ± 38	
Fibrinogen (mg/dl)	478 ± 197	470 ± 188	536 ± 284	–	

[a] FMF without amyloidosis < FMF having amyloidosis type 1 = FMF having amyloidosis type 2
[b] FMF without amyloidosis > FMF having amyloidosis type 1 = FMF having amyloidosis type 2
[c] FMF without amyloidosis < FMF having amyloidosis type 1 < FMF having amyloidosis type 2

Table 3 Accompanying diseases

Disease	Number of cases
Henoch-Schönlein purpura	10
Polyarteritis nodosa	9
Juvenile rheumatoid arthritis	9
Sacroiliitis	3
Right renal agenesis, polymyositis, peptic ulcer	two from each
von Willebrand disease, G6PD deficiency, thalassaemia trait, epilepsy, dermatomyositis, bronchial asthma, vesicoureteral reflux, mitral insufficiency	one from each

6.04 fold increased risk of amyloidosis ($P < 0.0001$) (Table 4). Amyloid-free survival is demonstrated in Table 5.

Total number of FMF patients put on colchicine therapy was 435, but 10 (2.3%) have developed amyloidosis during the follow up.

Among the 113 FMF patients having type I amyloidosis, 41 were lost to follow up, and 29 died during follow up. Twenty-six of the FMF patients having type II amyloidosis ($n = 57$) were lost to follow up, whereas 18 died during follow up. The time interval to develop chronic renal failure after the development of amyloidosis is displayed in Table 6.

Discussion

In our paediatric population the male/female ratio was higher in the amyloidosis group (111/69) than the FMF patients without amyloidosis (225/200). This result differs from the previous paediatric series [2, 6, 8]. The ratio of our amyloidosis population is rather similar to that previously reported in many non-paediatric series. This result is in favour of a protective role of the oestrogen hormone in the development of amyloidosis.

The frequency of abdominal pain in the FMF cases (95%) was similar to other studies (97%), whereas the

Table 4 Risk factors for the development of amyloidosis (*AFS* amyloidosis-free survival, *OR* odds ratio)

Factor	5-year AFS	10-year AFS	*P* value[a]	*P* value[b]	OR
Consanguinity and/or amyloidosis in family[c]				< 0.0001	
Both absent	86.3%	62.8%	–	–	
Consanguinity	87.7%	79.2%	0.70	0.47	1.05
Amyloidosis in family	68.9%	45.4%	0.002	0.01	2.37
Both present	52.6%	24.6%	< 0.0001	< 0.0001	6.04
Fever					
Yes	88.2%	75.9%	< 0.0001	0.0003	0.38
No	59.1%	21.0%			
Abdominal pain					
Yes	87.4%	72.4%	< 0.0001	< 0.0001	0.22
No	46.1%	14.1%			
Arthritis					
Yes	73.7%	53.5%	0.005	0.32	1.41
No	85.6%	68.6%			
Arthralgia					
Yes	80.9%	58.2%	0.28	0.32	0.71
No	84.3%	70.4%			
Chest pain					
Yes	87.1%	83.7%	0.13	0.06	0.40
No	82.1%	63.0%			
Sex[e]					
Female	84.4%	63.6%	0.36	0.84	0.95
Male	81.4%	65.6%			
Compliance					
Poor	93.8%	79.3%	0.23	0.32	0.61
Good	85.7%	68.7%			
Age at onset[d]	–	–	< 0.0001	< 0.0001	1.26
Age at diagnosis[d]	–	–	0.001	0.37	0.96

[a] Log rank test
[b] Cox regression model
[c] Reference group for odds ratio is "the patients with neither consanguinity nor amyloidosis in family"
[d] Reference group for odds ratio is "the patients 1 year younger"
[e] Reference group for odds ratio is "male patients"

Table 5 Median amyloid-free survival in FMF patients

Group	*n*	Median amyloid-free survival (years)	*P* [a]
Consanguinity (−), amyloidosis in family (−)	364	>20	–
Consanguinity (+), amyloidosis in family (−)	127	>22	0.70
Consanguinity (−), amyloidosis in family (+)	42	9.0	0.002
Consanguinity (+), amyloidosis in family (+)	35	6.3	0.0001

[a] *P* values correspond to pairwise comparison with "Consanguinity (−), amyloidosis in family (−)" group

Table 6 Analysis of time-to-chronic renal failure in amyloidosis patients (life-table analysis)

Duration of follow up after diagnosis (years)	Probability of developing chronic renal failure after diagnosis	
	Type 1 ($n = 123$)	Type 2 ($n = 57$)
1 year	17.1%	40.2%
3 years	42.3%	50.2%
5 years	56.9%	81.3%
10 years	77.1%	–
Median time to chronic renal failure (years)	4.8	3.0

frequency of fever was lower in our series compared to the relevant literature [5–7]; 0.5% of our FMF patients without amyloidosis and 22% of our FMF cases having amyloidosis type I failed to show fever and abdominal pain. The diagnosis of FMF in these patients was confirmed by the presence of a family history and response to colchicine treatment. This finding may be due to recognition bias (the unawareness of the family from the presence of fever during the attacks). Fever history is insistently sought in our centre for the diagnosis of FMF, and patients without fever history are always investigated for other criteria, especially during the attacks. Therefore, excluding recognition bias, the presence of atypical cases seems to be a more probable explanation for the lack of fever. Among the FMF patients having amyloidosis type I, the frequencies of fever and abdominal pain were 54% and 69%, respectively. This latter result can be explained by the overshadowing of the FMF-related symptoms by the renal-related symptoms. Appendectomy was as high as 7.1% in our series, whereas up to 49% of patients with FMF have been reported to have had laparotomy [15].

The association of FMF with various vasculitic diseases has been previously reported [3, 9]. We found 10 Henoch-Schönlein Purpura and 9 polyarteritis nodosa cases among our patients. The association of FMF and vasculitis awaits to be clarified and a common antigenic stimulus may well be the trigger for both. On the other hand, since cytokines are important elements in the pathogenic process of both of these diseases, an upregulation in the genes of certain cytokines or receptors may be an alternative explanation [10]. Other diseases found in our FMF patients are likely to be coincidental (Table 3).

An important point that we had previously indicated in our preliminary results, and that we demonstrate again is the significantly high frequency of amyloidosis development in those patients with a positive family history for amyloidosis ($P = 0.00001$) [13]. The presence of a familial history of amyloidosis has indeed been defined as the most important risk factor in the development of amyloidosis among our patients. Presence of consanguinity was another important predictor; consanguinity plus a familial amyloidosis increased the odd's ratio to 6.04 (Table 4). Again the presence of another familial index case of amyloidosis had the most marked influence on the duration of the development of renal failure. These results suggest that additional genetic markers may be efficacious in the development of the secondary amyloidosis. It has been already demonstrated that the FMF gene maps to the short arm of chromosome 16 in the major ethnic groups affected by FMF. However, genetic studies on the secondary amyloidosis of FMF are lacking.

It was also noted that younger age at diagnosis defined a negative risk which may be explained by the beneficial effect of therapy. Only 2.3% of the patients who were treated with colchicine developed amyloidosis. This figure is similar to our preliminary study [13]. Zemer et al. [16] have stated that none of their patients develop amyloidosis after colchicine. We had previously shown that increased $beta_2$-microglobulin excretion and microalbuminuria during the attacks decreases after colchicine administration, however the mechanism of its effect remains to be elucidated [14]. We believe that persistent microalbuminuria and $beta_2$-microglobulinuria may indeed be early markers for renal amyloidosis as in diabethic nephropathy.

Progress to end-stage renal failure differs between type I and type II amyloidosis patients; in type II amyloidosis uraemia is reached in 5.1 years whereas this duration is 10

years in type I amyloidosis. Thus type II amyloidosis has a worse prognosis as compared to type I (Table 6).

We conclude that in the paediatric FMF population male sex, family history for amyloidosis, consanguinity, arthritis, persistent microalbuminuria, and beta$_2$-microglobulinuria are the predisposing and predicting factors for amyloidosis. Earlier diagnosis (earlier onset of disease) with earlier initiation of colchicine therapy seem to protect from amyloidosis. The genetic factors which regulate these processes still remain to be discovered.

References

1. Cox DR (1972) Regression models and life tables. JR Stat Soc Series B 34:187–220
2. Gedalia A, Adar A, Gorodischer R (1992) Familial Mediterranean fever in children. J Rheumatol 19 [Suppl 35]:1–9
3. Glikson M, Galun E, Schlesinger M, Cohen D, Haskell L, Rubinow A, ELaikim M (1989) Polyarteritis nodosa and familial Mediterranean fever: a report of two cases and review of the literature. J Rheumatol 16:536–539
4. Goldfinger SE (1972) Colchicine for familial Mediterranean fever (Letter). N Engl J Med 287:1302
5. Heller H, Sohar E, Sherf L (1958) Familial Mediterranean fever. Arch Intern Med 102:50–71
6. Ludomirsky A, Passwll J, Boichis H (1981) Amyloidosis in children with familial Mediterranean fever. Arch Dis Child 56:464-467
7. Majeed HA, Barakat M (1988) Familial Mediterranean fever (recurrent hereditary polyserositis) in children: analysis of 88 cases. Eur J Pediatr 148:636–641
8. Majeed HA, Caroll JE, Khuffash FA, Hijazi Z (1990) Clinical and laboratory observations. Longterm colchicine prophylaxis in children with familial Mediterranean fever (recurrent hereditary polyserositis). J Pediatr 116:997–999
9. Ozen S, Saatçi Ü, Balkanci F, Besbas N, Bakkaloglu A, Tacal T (1992) Familial Mediterranean fever and polyarteritis nodosa. Scand J Rheumatol 21:312–313
10. Özyilkan E, Simsek H, Telatar H (1992) Tumor necrosis factor in familial Mediterranean fever. Am J Med 92:579
11. Peto R, Pike MC, Armitage P, et al (1977) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II Analyses and examples. Br J Cancer 35:1–39
12. Rogers DB, Shohat M, Petersen GM, et al (1989) Familial Mediterranean fever in Armenians: Autosomal recessive inheritance with high gene frequency. Am J Med Genet 34:168–172
13. Saatçi Ü, Bakkaloglu A, Ozen S, Besbas N (1993) Familial Mediterranean fever and amyloidosis in children. Acta Paediatr 81:705–706
14. Saatçi Ü, Özdemir S, Ozen S, Bakkaloglu A (1994) Serum concentration and urinary excretion of β_2-microglobulin and microalbuminuria in familial Mediterranean fever. Arch Dis Child 70:27–29
15. Schwabe AD, Peters RS (1974) Familial Mediterranean fever in Armenians: analysis of 100 cases. Medicine 53:453–462
16. Zemer D, Livneh A, Danon YL, Pras M, Sohar E (1991) Long-term colchicine treatment in children with familial Mediterranean fever. Arthritis Rheum 34:973–977