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Familial Mediterranean fever in children: the expanded clinical profile

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Summary

The clinical picture of familial Mediterranean fever (FMF) has been appreciably expanded in the last 10 years. Over 8 years, we studied the expanded clinical profile of FMF in 476 children. Of these, 81% had abdominal pain, 41% chest pain, 42% arthritis, 12% severe myalgia, 12% skin manifestations, 4% scrotal swelling, 3% recurrent episodic fever, and one child (0.2%) developed recurrent hyperbilirubinaemia. Two (0.4%) children developed renal complications which were reversed by colchicine; however of 19 probands, 36 family members suffered from chronic renal failure. Our study indicates a familial predisposition to nephropathy in certain families with FMF. This study is the first to report the expanded clinical profile of FMF in a large group of Arab children, giving an opportunity to compare the findings with those in children with FMF in other ethnic groups, and to help in the study of genotype-phenotype correlation.

Introduction

Familial Mediterranean fever (FMF), also known as familial paroxysmal polyserositis[1] or recurrent hereditary polyserositis,[2] is a genetic multisystem disease, characterized by recurrent self-limiting painful episodes of sterile peritonitis, plueritis and arthritis. The clinical picture of FMF has been expanded appreciably in the last 10 years, when additional features have been described, including severe myalgia,[3] the protracted febrile myalgia syndrome,[4] scrotal swelling[5] and cardiac involvement.[6]

The striking feature of the disease is that it affects certain ethnic groups disproportionately, mainly Arabs, Jews, Armenians and Turks.[2] The disease-causing gene *MEFV* has been mapped by linkage analysis to the tip of the short arm of chromosome 16.[7,8] The *MEFV* gene was cloned by two independent groups, and several mutations were identified in its sequence.[9,10] The protein encoded by the gene was termed 'pyrin' and 'marenostrin' by the two groups.[9,10] One mutation was found more frequently in populations with a higher incidence of systemic amyloidosis, whereas another mutation was found in a population in which amyloidosis was less common.[9] Familial Mediterranean fever is common in Arabs.[2,11–13] The main aim of this study was to delineate the expanded clinical profile (phenotype) in a large group of Arab children, and to compare the results with those for other ethnic groups at risk.

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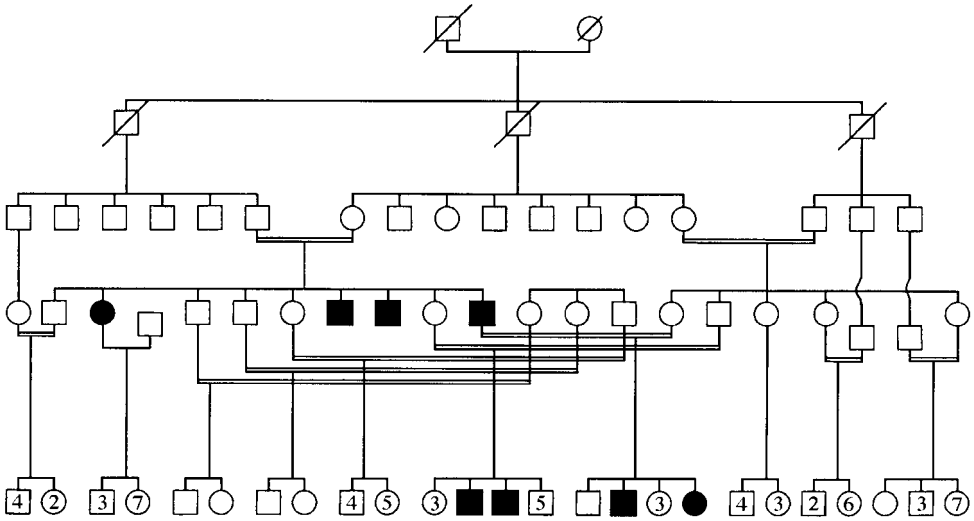

Figure 1. Pedigree of a family with FMF, showing the pseudodominant pattern of inheritance due to extensive inbreeding, as evidenced by the multiple consanguinity loops. It also shows the absence of nephropathy as a complication of FMF in this family. Filled symbols indicate FMF.

Methods

From January 1991 through December 1998, 476 children with FMF were seen in the pediatric FMF clinics of the teaching hospitals of the Faculties of Medicine, University of Jordan (Mid Jordan) and Jordan University of Science and Technology, Irbid (North Jordan). The children were referred from the primary health-care centres by their family physicians, and information was obtained from the parents in the presence of their children.

The following tests were performed on all children: haemoglobin; white cell count; platelets; erythrocyte sedimentation rate; urine microscopy and culture; stool analysis and culture; abdominal ultrasound; Widal and brucella agglutination tests; and kidney and liver function tests. Other investigations performed when necessary included haemoglobin electrophoresis, endoscopy, barium meal and follow-through, plane chest and bone radiography, tests for antinuclear antibodies, C3, C4 and CH50, hepatitis B surface antigen, rubella virus IgM antibodies, rheumatoid factor, antistreptolysin O titre, immunoglobulins, creatine phosphokinase (CPK), electromyography (EMG), technetium bone scan, bone-marrow biopsy, and CT abdominal scans. Serum IgD level was assessed in 93 patients with FMF and 53 healthy children.

Follow-up

Children were seen from once weekly to every 3 months, according to the individual child.

Diagnostic criteria

Diagnosis of FMF was based on the criteria of Heller *et al.*[14] These are: (i) short attacks of fever recurring at varying intervals; and (ii) absence of any causative factor or pathological finding capable of explaining the clinical picture. However, of the completed data collection study forms of the children with FMF, 175 forms were randomly selected and subjected to the criteria recently described by Livneh *et al.*[15] All satisfied the criteria. Myalgia was defined as pain and/or tenderness in the extremities away from the joints, in the absence of joint swelling and signs of underlying osteomyelitis. Exercise-induced myalgia was defined as myalgia with an onset within 6 h of exercise. Spontaneous myalgia was defined as myalgia not related to exercise or any other precipitating factor. The protracted febrile myalgia syndrome was defined according to previously reported criteria.[4]

Results

Over a period of 8 years, 476 children with FMF were seen; 221 (46%) were boys and 255 (54%) were girls. All children were Arabs of Jordanian and Palestinian origin.

Family history

A positive family history was present in 279 children (59%). In many families, transmission of the disease occurred in three successive generations (Figures 1 and 2).

Age at onset

The peak onset was between the ages of 2 and 10 years (Table 1). Ninety-five children (20%) were symptomatic below the age of 2 years, and in 411 (86%) the disease started below the age of 10 years.

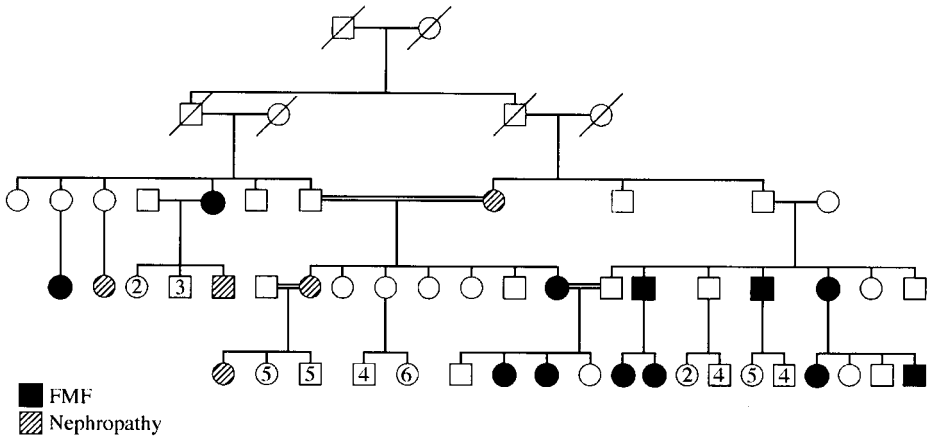

Figure 2. Pedigree of a family with FMF, showing predisposition to nephropathy. It also shows the pseudodominant pattern of inheritance.

Serum IgD levels

Of 93 patients with FMF, 13 (14%) had serum IgD >60 mg/l. Of these, seven had levels >100 mg/l and five had >141 mg/l. Mean serum IgD in the 93 patients was 29.5 mg/l. However, in patients whose IgD was checked twice, the mean (of two readings) was 45.7 mg/l, whereas the mean level in 53 normal healthy children was 12.5 mg/l.

Presenting features

Abdominal pain was the most common presenting feature (Table 2). Fifteen (3%) children presented with recurrent episodic fever without serositis. The episode lasted 1–5 days with spontaneous remission; nine children subsequently developed serositis 1.5 to 3 years after the onset of fever. Of the six patients who did not develop serositis, five patients had a family history of FMF. The response to colchicine was dramatic in all. Colchicine therapy was refused by the mother of one child. All six children had normal serum levels of IgD.

Clinical profile

Recurrent abdominal pain was the most common feature (Table 3). In many patients it was generalized, whereas in others it was localized to the left or right renal angle (most of these patients had peritoneopleural attacks), or in the left or right iliac fossae; in a few patients the pain was mainly suprapubic. Generally, the pain was severe and occurred in clusters lasting for 15–60 min over a period of 1–3 days; in the majority of children, the attacks were associated with fever, which was mild, moderate or high.

The chest pain was generally unilateral, mainly on the left side and was pleuritic in nature, lasting for 1–3 days. Arthritis was mainly recurrent monoarticular involving a large joint, mainly the knee or ankle (Table 4). Other clinical patterns of arthritis included simultaneous symmetrical two-joint arthritis, symmetrical polyarticular (juvenile rheumatoid arthritis type), assymetrical oligoarticular (acute rheumatic fever type), sacroiliac joint involvement (ankylosing spondylitis type) and small joints of the hands and feet (Table 4). Cutaneous manifestations developed in 57 children (12%) (Table 3). These included the erysipelas-like erythema, recurrent purpuric rash, maculopapular rash, urticaria and angioneurotic oedema, Henoch-Schönlein purpura, and (in one) panniculitis.

Seventeen children (4%) developed 29 episodes of scrotal swelling and was the presenting feature in

Table 1 Age at onset in 476 children with FMF

Age (years)	*n* (%)
<2	95 (20)
2–5	163 (34)
6–10	153 (32)
>10	65 (14)
Total	476 (100)

Table 2 The presenting features in FMF in 476 children

Feature	*n* (%)
Abdominal pain	267 (56)
Arthritis	103 (22)
Chest pain	71 (15)
Episodic fever	15 (3)
Myalgia	16 (3)
Scrotal swelling	4 (1)
Total	476 (100)

Table 3 The clinical profile of FMF in children of four ethnic groups

Feature	Lehman *et al.* (31 Armenians)	Yalcin-Kaya *et al.* (110 Turks)	Gedalia *et al.* (101 Jews)	Present study (476 Arabs)
Abdominal pain (%)	90	88	90	81
Chest pain (%)	62	35	23	41
Arthritis (%)	80	19	61	42
Skin (%)	7	11	34	12
Scrotal swelling (%)	–	–	8	4
Myalgia (%)	–	–	13	11
Jaundice (%)	–	–	–	0.2
Episodic fever (%)	–	–	–	3

Table 4 The clinical patterns of FMF arthritis

Pattern	Joint affected		No. of patients
Monoarticular	Knee		87
	Ankle		40
	Hip		5
	Elbow		4
	Wrist		2
	Shoulder		1
		Subtotal	140 (70%)
Simultaneous symmetric two-joint arthritis	Both knees		14
	Both ankles		8
	Alternating		7
		Subtotal	29 (15%)
Polyarticular symmetric	JRA-like		7
Oligoarticular asymmetric	JRA-like		5
		Subtotal	12 (6%)
Oligoarticular asymmetric	ARF-like		7 (3.5%)
Small joints of the hands			8 (4%)
Small joints of the feet			2 (1%)
Sacroiliac joint	AS-like		1 (0.5%)
		Total	199 (100%)

four (1%). It was unilateral in 27 and bilateral in two. Four children who were on regular colchicine prophylaxis developed scrotal swelling. The scrotum was explored in five patients. The operative findings were available in three and showed normal testes and epididymis, inflamed tunica vaginalis and the presence of exudative fluid in one. One of our patients developed recurrent hyperbilirubinemia in the course of FMF, with an excellent response to colchicine (Table 3).

Fifty-two children (11%) developed severe myalgia (Table 3) and in 16, myalgia was the presenting feature (Table 2). The mean ages at onset of FMF and myalgia were 5.2 and 7 years, respectively. Three main patterns could be delineated, which differed in pain severity and duration. Five children developed the protracted febrile myalgia syndrome; the pain was excrutiating and lasted for about 6 weeks. Forty-two children developed exercise-induced myalgia; the pain was severe and lasted for 1–3 days. Five children developed spontaneous myalgia; the pain was mild to moderate and lasted for about 8 h.

Electromyography (EMG) was performed in four children with exercise-induced myalgia and one with the protracted febrile myalgia syndrome. The findings showed no definite abnormal spontaneous activity in four; however, in one patient, exercise-induced insertional activity was detected. CPK was determined in 26 patients and was normal in all.

Surgery

Eighty-nine children (19%) were subjected to surgery, of whom 54 had laparatomy and appendectomy, 15 had tonsillectomy, 13 had arthrotomy, two synovectomy, and the scrotum was explored in five children.

Amyloidosis

One child developed proteinuria alone and one developed haematuria and proteinuria. The first was referred at the age of 8 years with recurrent abdominal pain of 3 years duration and proteinuria of a few months duration. There was no family history of FMF. Her blood pressure was normal and she had no oedema. Serum albumin and creatinine were normal, but urine examination showed proteinuria $++++$. She was put on colchicine 0.5 mg twice daily; examination of her urine 1, 3 and 12 months later showed no proteinuria. The second child was referred at the age of 12 years with 'a few years' history of recurrent abdominal pain and 'a few months' history of microscopic haematuria. There was a family history of FMF. On examination, he looked normal and healthy, blood pressure was normal, oedema was absent. Urine examination revealed gross microscopic haematuria and proteinuria $++$. He was put on clochicine 1.5 mg daily; urine examination 1, 3 and 6 months later revealed no microscopic haematuria or proteinuria. He had no further attacks of abdominal pain. We were able to collect information about 19 families of the probands, which revealed 36 members affected with chronic renal disease following recurrent abdominal pain, chest pain or arthritis. Some families had 1–2 members affected, other families had more. The majority of the affected family members were above the age of 18 years. One family had seven members with chronic renal disease; three died and four were on peritoneal dialysis. Another family had five affected members; one died and two of the other four were on dialysis. All had the various manifestations of FMF. Of this family, we had the chance to examine a 45-year-old lady with chronic renal disease following 'many years' of recurrent abdominal and chest pain. Her blood pressure was high but she had no oedema. Her serum creatinine was very high and urine examination and culture showed gross haematuria and proteinuria $++$ but no growth. Ultrasound abdomen showed no cystic changes and normal-sized kidneys. Renal biopsy and investigation of the rest of the family, were refused, mainly because of expenses. Figure 1 shows the family with five affected members. Figure 2 shows the family tree of another family with strong history of FMF but no chronic renal disease.

Treatment

Colchicine was prescribed to all patients. The doses used were the same as reported by us earlier.[19] Generally children aged 5 years or less needed 0.5 mg daily, those between 5–10 years 1 mg daily and 1.5 mg daily in children above 10 years. Very few patients needed 2 mg daily to suppress their symptoms. The response to colchicine was favourable in 96% of patients, and it was well tolerated by all. One adverse effect was diarrhoea, which occurred in few patients and ceased when the dose was reduced and more gradual increment was followed. Two girls developed alopecia; one proved to have juvenile rheumatoid arthritis and the hair was back to normal 1 month after stopping colchicine, the other girl was lost to follow-up.

Discussion

The large number of patients in this series points to the high prevalence of FMF in Jordan. Previously we reported a prevalence of 1:2600 and a gene frequency of 1:50 in the childhood population of Jordan,[12] which was similar to the prevalence of 1:2000 and gene frequency of 1:45 reported by Sohar in 1967 in Israel.[20] However, recent studies by Daniels *et al.*[21] and Rogers *et al.*[22] using information collected on uncles, aunts and cousins of the probands, estimated a high gene frequency of 1:6 and 1:12 in Sephardic and Ashkinazi Jews, respectively, and 1:7 in Armenians. We believe that the true prevalence in Jordan is higher than estimated. This is based on the low index of suspicion, as shown by the long mean diagnostic delay,[12] the 64% consanguinity rate of all marriages in Jordan[23] and the presence of pedigrees showing pseudodominent inheritance. Linkage analysis mutation detection and complex segregation analysis studies would reflect the true prevalence.

The clinical picture of FMF has been appreciably expanded in the last 10 years.[3–6] Recently, the FMF gene was cloned, and four mutant genes were identified by the International and French consortia.[9,10] These findings suggested that different genotypes could result in different phenotypes. This study is the first to report the expanded clinical profile of FMF in a large group of Arab children, seen over a period of 8 years, giving the opportunity for comparison with children from other ethnic groups at risk.

Our findings showed a slight female preponderance, with a female:male ratio of 54% to 46%, which is the same as reported by us previously,[12] and does not support the suggestion that FMF may have incomplete penetrance in females.[24]

Of the 476 children, 199 (42%) developed arthritis, which is similar to our previous study of arthritis in children with FMF.[13] The incidence among Jewish children (75%) and adults (74%) was significantly higher than that reported in Arabs, Turks and Armenians.[2,11,13,20,25–28] (Table 5). However, this could be due to under-reporting in these ethnic groups. According to Yazici and Ozdogan, 'even in

Table 5 Incidence of FMF arthritis in different ethnic groups

Author (year)	Reference	No. with FMF	Main age group	Ethnic group	No. with arthritis (%)
Sohar *et al.* (1967)	20	470	Adults	Jews	346 (74)
Schwabe & Peters (1974)	26	100	Adults	Armenians	37 (37)
Barakat *et al.* (1986)	2	175	Adults and children	Arabs	59 (34)
Ozdemir & Sokemen (1969)	25	57	Adults	Turks	25 (44)
Zemer *et al.* (1991)	27	334	Children	Jews	251 (75)
Majeed & Barakat (1989)	11	88	Children	Arabs	44 (50)
Majeed & Rawashdeh (1997)	13	336	Children	Arabs	133 (40)
Yazici & Ozdogan (1997)	28	544	Adults	Turks	303 (56)
Present study		476	Children	Arabs	199 (42)

a country (Turkey), where the disease is more or less common, it takes a mean of 7 years before the diagnosis of FMF is made'.[30] However, a general difference in the genotype/phenotype amongst the four ethnic groups remains a real possibility.

Recurrent episodic fever was the presenting feature in 15 (3%) patients (Table 2). The presentation with fever alone imposes a difficult diagnostic problem. Two diseases mimicking FMF should be excluded; namely the hyper IgD syndrome (HIDS) and Behçet's disease, as both may present with recurrent episodic fever.[29–31] The episode usually lasts for 1–3 days in FMF, whereas it lasts for around a week or more in HIDS and longer in Behcet's disease.[31–33] The response to colchicine is usually excellent in FMF, but poor in HIDS. Although colchicine is used as an anti-inflammatory agent in Behçet's disease and other diseases associated with inflammation and fibrosis, the response is slow, and limited; quite different from the rapid and remarkable response in patients with FMF. The diagnostic work-up of recurrent episodic fever is frustrating to the child, family and the paediatrician. In a recent report, we suggested that in a similar situation where the patient is from an ethnic group at risk, namely Arabs, Jews, Armenians or Turks, and is well between attacks, and especially in the presence of a positive family history of FMF, a therapeutic test of colchicine for a few months could be rewarding.[32] Our present and previous data, together with those of Hallabe *et al.*[33] support this concept. This will avoid delay in the initiation of colchicine prophylaxis and the risk of renal failure.

Seventeen (4%) patients developed 29 episodes of scrotal swelling (Table 3). Eshel *et al.* were the first to report the new entity of acute scrotal swelling as a feature of FMF.[5] Our experience and that of Eshel *et al.*, showed that there were information and clinical findings which could help to differentiate this new entity from testicular torsion. The gradual onset of fever (usually mild to moderate), and pain (usually mild to moderate), more than 8 h from the onset, the presence of recurrence(s), in a child from an ethnic group at risk and especially in the presence of positive family history of FMF, were helpful diagnostic clues.[5] The hallmark of FMF is recurrent febrile serositis. It should not therefore be surprising that the tunica vaginalis (a serosal membrane) is involved in the course of FMF; the duration of the attack is similar to that seen in peritonitis, pleuritis and the majority of children with synovitis. However, it was surprising that inflammation of the tunica vaginalis, which is an extension of the peritoneal sac, occurred in the absence of peritonitis in all our patients. Acute scrotal swelling developed in four (24%) children who were on regular prophylaxis. This failure rate is much higher than the 3% failure reported by us earlier.[12] Similarly, eight (28%) of the children reported by Eshel *et al.* developed scrotal swelling while on regular colchicine prophylaxis.[5] These high failure rates are alarming, since the patient reported by Livneh *et al.* developed testicular necrosis following recurrent scrotal attacks.[34] The absence of scrotal swelling as a feature of FMF in many series (Table 3) is probably only a reflection of its recent recognition as a feature of FMF.

The exercise-induced pattern of myalgia was more common than the others. In these children, the pain was severe and the episode lasted for 1–3 days, similar to the duration of the other serosal attacks of FMF. Furthermore, the response to colchicine was also similar, with a success rate of 97%. The EMG changes were those of mild inflammatory myopathy, and were similar to the experience of Langevitz *et al.*, where the EMG findings, performed on three patients, showed non-specific inflammatory myopathy.[4]

One of our patients developed recurrent hyperbilirubinaemia in the course of FMF, and had an excellent response to colchicine. In the early 1950s, the French investigators Cattan and Bloede were the first to report hyperbilirubinaemia as a feature of FMF.[35,36] This was followed by the reports of Priest and Nixon, Reiman and Seigal.[37,38,1] Of the eight

patients described by Althausen *et al.* under the title 'the acute false abdomen' which was almost certainly FMF, two developed jaundice.[39] Hyperbilirubinaemia of FMF seems to have a distinct clinical picture; it occurs only during a peritoneal attack, and not with other attacks, and never as an isolated phenomenon. It is transient, lasting for 1–2 days, and the jaundice is clinically mild with a minimal rise of bilirubin (mainly direct). Of the two patients described by Reiman, 'jaundice was not remembered or recorded in the histories of either patient.'[38] Similarly, of the six patients with increased serum bilirubin described by Priest and Nixon, only three were clinically recognized as icteric.[37] This could explain the absence of this feature in the large series published after the 1960s, including Sohar *et al.*,[20] Armenian and Khachadorian,[40] Schwabe and Peters,[26] Barakat *et al.*,[2] Majeed and Barakat[11] and Yazici and Ozdogan.[28] Since the early 1960s, only two patients with FMF and recurrent hyperbilirubinaemia were reported, in 1994 and 1998.[41,42]

Data from this study show a very low incidence of chronic renal disease complicating FMF (Table 6) and are in agreement with our earlier reports[11,12] which were also conducted in the 'colchicine era.' The two children affected in the present study were not on colchicine prophylaxis; they had an excellent response to colchicine, mainly because of an early presentation, before reaching the nephrotic phase, confirming earlier reports.[43,44] The family studies strongly point towards a familial predisposition to nephropathy in certain families with FMF (Figures 1 and 2), and strongly support the early pioneering reports by Cattan and Mamou, who found 'predisposition to progressive nephropathy in familial paroxysmal polyserositis to be particularly marked in certain families'.[45] They are also in agreement with those of Saatci *et al.*, who reported that the presence of a family history of amyloidosis plus consanguiuity had a 6.04-fold increased risk of amyloidosis.[46]

Table 6 Incidence of amyloidosis complicating FMF among different ethnic groups

Ethnic group (number)	Amyloidosis (%)	Reference
Arabs (88 children)	2	11
Arabs (175, mainly adults)	1.7	2
Arabs (41, adults)	0	47
Arabs (120, mainly adults)	10.1	40
Sephardic Jews (470)	26.5	20
Sephardic Jews (401)	42	48
Sephardic Jews (95)	12	49
Armenians	24	50
Armenians (100)	0	26
Turks (57)	60	25
Turks (25)	60	51
Turks (544)	7	28
Present study (Arabs) (476)	0.4	

Many studies have claimed clinical heterogeneity of FMF amongst the various ethnic groups at risk. Table 6 clearly shows that Jewish patients, in contrast to the other three ethnic groups, had an increased incidence of amyloidosis. These differences could be due to many factors, including patient selection, chance variation and different diagnostic standards, especially in the absence, so far, of a specific diagnostic test, or due to genotype-phenotype differences. There has been considerable disagreement among various investigators on the incidence of secondary amyloidosis complicating FMF, even within the same ethnic group (Table 6). In 1967, Sohar *et al.* from Israel reported an incidence of 26.5%, but claimed that amyloidosis leaves few survivors above the age of 40 years,[20] whereas Gafni *et al.* also from Israel reported 42% in 1968[48] and Eliakim 12% in 1970,[49] (Table 6). Similarly, the incidence of amyloidosis in Armenians varied between 0% in the USA[28] and 24% in Russia.[50] Furthermore, the incidence of amyloidosis in Arabs varied between 0% and 10.1%. The low incidence of 1.7% and 2% in Arab patients reported by Barakat *et al.*[2] and Majeed and Barakat,[11] could be due to the fact that both studies were conducted in the colchicine era (Table 6). The incidence among the Turks varied between 7% and 60% (Table 6). It is tempting to assume that these variations are examples of clinical heterogeneity among the different ethnic groups. However, the wide variations reported within the same ethnic group and almost at the same period of time (Table 6), do not support this possibility. Patient selection is very obvious in the Turkish figures (Table 6), where a very high incidence of 60% was reported from tertiary renal referral centres.[25,51] Recently, in a group of 544 Turkish patients, Saatci *et al.* reported an incidence of 7%.[28] Another factor is the lack of an adequate period of observation for many of the patients that have been reported. According to Mayerhof[52] 'even a seemingly adequate period may not be long enough, Bakir and Murtada[47] reported 41 patients without amyloidosis seen over a period of 10 years. Subsequently, one of their original patients developed amyloidosis and another case occurred among new patients.'

However, with the recent identification of mutant genes, new though preliminary data on genotype-phenotype correlations started to emerge. These data revealed that the severe course of FMF correlated with homozygosity for M694V, the mutation found in 94% of North African Jews.[53] In M694V homozygotes, FMF was characterized by an earlier onset, more frequent attacks, more joints affected and requirement for a higher dose of colchicine.[53] Also,

amyloidosis was found in 12/70 FMF patients who were homozygous for M694V, but in none of 13 heterozygotes for this mutation, or carrying the V726A mutation.[54]

A recent study by Shohat *et al.* demonstrated a significant association between a specific haplotype at the MEFV locus and amyloidosis in FMF.[55] Further genotype-phenotype studies in the four ethnic groups are needed. It may be worth stressing that we have not detected phenotype II in any of our patients or their family members with amyloidosis. This cannot obviously be due to colchicine, as phenotype II presents with amyloidosis without a preceding history of serositis.[20] Our findings support those of Yazici and Ozdogan, who screened 297 relatives of nine patients with FMF and could not give support to the concept of phenotype II.[28] The low incidence (0.4%) of renal disease secondary to FMF in our patients is almost certainly due to the use of colchicine. This is supported by the fact that the majority of the affected family members are above the age of 18 years, mostly between the age of 30–45 years, and did not receive colchicine prophylaxis.

An interesting finding in this study was the 45-year-old lady whose chronic renal disease presented with gross microscopic haematuria and mild proteinuria. Ultrasound of the abdomen showed no cystic renal changes and normal-sized kidneys, which ruled out polycystic disease of the kidney and amyloid nephropathy. Non-amyloid glomerular disease as a complication of FMF has been reported earlier. Eliakim *et al.* detected renal lesions in 34% of 106 Jewish patients with FMF, of whom 12.3% had amyloidosis and 21.7% had non-amyloid nephropathy.[49] Of the 15 Arab patients with FMF and nephropathy reported by Said *et al.*, seven had amyloidosis, six had mesangio-proliferative glomerulonephritis, and two had rapidly progressive glomerulonephritis.[56]

The clinical picture of the recently-described hyper IgD and periodic fever syndrome (HIDS), has striking similarities to FMF.[29,30] The high serum IgD level was defined as >160 IU (141 mg/l) by Van der Meer *et al.* and Drenth *et al.*,[29,30] whereas it was defined as >60 mg/l in two other studies.[57,58] It is interesting that of the 93 patients in this report, thirteen (14%) had serum IgD levels >60 mg/l and five (5.4%) >141 mg/l. This is similar to the findings of Livneh *et al.*; of 70 patients with FMF, nine (13%) had high levels >141 mg/l.[59] Our findings and those of Livneh *et al.* pose difficulties in the diagnosis of FMF and HIDS. However, advances in molecular genetics are expected to overcome these difficulties, as the location of the gene causing HIDS is different from that of FMF.[60] Furthermore, a rapid cost-effective test was reported to be highly reliable for detecting common mutations in FMF.[61]

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References

1. Siegal S. Familial paroxysmal polyserositis. Analysis of fifty cases. *Am J Med* 1964; **36**:893–920.
2. Barakat M, Karnic AM, Majeed HA, El-Sobki N, Fenech F. Familial Mediterranean fever (recurrent hereditary polyserositis) in Arabs. A study of 175 patients and review of the literature. *Q J Med* 1986; **60**:837–46.
3. Kuhreich E, Naschitz IE, Khon A, Yeshuran D. Familial Mediterranean fever presenting with recurrent severe myalgia. *Harefueh* 1984; **106**:209–10.
4. Langevitz F, Zemer D, Livneh A, Shemer J, Pras M. Protracted febrile myalgia syndrome, in patients with familial Mediterranean fever. *J Rheumatol* 1994; **21**:708–9.
5. Eshel G, Vinograd I, Barr J, Zemer D. Acute scrotal pain complicating familial Mediterranean fever in children. *Br J Surg* 1994; **81**:894–6.
6. Guindo J, Rodriguez A, Ramio J, Miguel Diaz MA, Subirana MT, Peres Ayuso MJ, Cosin J, Bayes AL. Recurrent pericarditis: Relief with colchicine. *Circulation* 1990; **82**:1117–20.
7. Pras E, Askentijevich I, Gruberg L, Balow J, Prosen L, Dean M. Mapping of a gene causing familial Mediterranean fever to the short arm of chromosome 16. *N Engl J Med* 1992; **326**:1509–13.
8. Pras E, Askentijevich I, Levy E, Gruberg L, Prosen L, Dean M. The gene causing familial Mediterranean fever maps to the short arm of chromosome 16 in Druze and Moslem Arab families. *Hum Genet* 1994; **94**:576–7.
9. The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; **90**:797–807.
10. The French FMF Consortium. A candidate gene for familial Mediterranean fever. *Nature Genetics* 1997; **17**:25–31.
11. Majeed HA, Barakat M. Familial Mediterranean fever (recurrent herediatary polyserositis in children. Analysis of 88 cases. *Eur J Pediatr* 1989; **148**:636–40.
12. Rawashdeh M, Majeed HA. Familial Mediterranean fever in Arab children: the high prevalence and gene frequency. *Eur J Pediatr* 1996; **155**:540–4.
13. Majeed HA, Rawashdeh M. The clinical patterns of arthritis in children with familial Mediterranean fever. *Q J Med* 1997; **90**:37–43.
14. Heller H, Sohar E, Sherf L. Familial Mediterranean fever. *Arch Intern Med* 1958; **102**:50–6.
15. Livneh A, Langevitz P, Zemer D, Kees S, Lidar T. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; **40**:1879–85.
16. Lehman TJA, Peters RS, Hanson V. Diagnosis and treatment of familial Mediterranean fever in childhood. *Arthritis Rheum* 1978; **21**:573–5.
17. Yalcin Kaya F, Tumer N, Tekin M, Sakar N, Aksakus M.

Familial Mediterranean fever in Turkish children (Analysis of 110 cases). In Sohar E, Gafni J, Pras M, eds. *Proceedings of the First International Conference on FMF*. London and Tel Aviv, Freund Publishing House, 1997:157–61.

18. Gedalia A, Adar A, Gorodischer R. Familial Mediterranean fever in children. *J Rheumatol* 1992; **35**:1–9.
19. Majeed HA, Carol J, Khuffash F. Long term colchicine prophylaxis in children with familial Mediterranean fever. *J Pediatrics* 1990; **116**:997–9.
20. Sohar E, Gafni J, Heller H, Pras M. Familial Mediterranean fever. A survey of 470 cases, and review of the literature. *Am J Med* 1967; **43**:227–52.
21. Daniels M, Shohat T, Brenner-Ulman A, Shohat M. Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish population in Israel. *Am J Med Genet* 1995; **55**:311–14.
22. Rogers D, Shohat M, Petersen G, Bickal J, Congleton J, Schwabe A, Rotter J. Familial Mediterranean fever in Arminians, recessive inheritance with high gene frequency. *Am J Med Genet* 1989; **34**:168–72.
23. Al-Salem M, Rawashdeh N. Consanguinity in North Jordan. *J Biosoc Sci* 1993; **25**:553–6.
24. Shohat M, Danon YL, Rotter JI. Familial Mediterranean fever. Analysis of inheritance and current linkage data. *Am J Med Genet* 1992; **44**:183–8.
25. Ozdimer AL, Sokmen C. Familial Mediterranean fever in Turkish people. *Am J Gastroenterol* 1969; **51**:311–16.
26. Schwabe AD, Peters RS. Familial Mediterranean fever in Armenians. Analysis of 100 cases. *Medicine* 1974; **53**:453–62.
27. Zemer D, Livneh A, Danon YL, Prasm, Sohar E. Long term colchicine treatment in children with familial Mediterranean fever. *Arthritis Rheum* 1991; **34**:973–7.
28. Yazici H, Ozdogan H. Familial Mediterranean fever in Turkey. In Sohar E, Gafni J, Pras M, eds. *Proceedings of the First International Conference of FMF*. London and Tel Aviv, Freund Publishing House, 1997:66–71.
29. Van der Meer JWM, Vossen JM, Radl J, Van Nieuwkoop JA, Meyer CJLM, Lobatto S, Van Fruth R. Hyperimmunoglobulinemia D and periodic fever syndrome. *Lancet* 1984; **i**:1087–90.
30. Drenth PHJ, Haagsma GJ, Van der Meer JWM and the International Hyper IgD Group. Hyperimmunoglobulinemia D and periodic fever syndrome: the clinical spectrum in a series of 50 patients. *Medicine* 1994; **73**:133–48.
31. Ghayad E, Tohme A. Behçet's disease in Lebanon: report of 100 cases. *Leb Med J* 1995; **43**:2–7.
32. Majeed HA, Rawashdeh M, Qubain H. Recurrent episodic fever: a presenting feature of familial Mediterranean fever. *Leb Med J* 1998; **46**:12–15.
33. Jose Halabi-Cherem, Islas-Arnade S, Lifshits A. Persistent fever as the only symptom of familial Mediterranean fever. *Arch Intern Med* 1990; **150**:1347.
34. Livneh A, Madgar I, Langevitz P, Zemer D. Recurrent episodes of acute scrotum with ischemic testicular necrosis in a patient with familial Mediterranean fever. *Am J Urol* 1994; **151**: 431–2.
35. Cattan R. Maladie periodique. Dix observations et deux hypothesis. *Bull Mem Soc Med Hop Paris* 1954; **70**:43–50.
36. Bloede G. Maladie periodique et rythms biologiques. *Maroc Med* 1954; **33**:7–14.
37. Priest R, Nixon RK. Familial recurring polyserositis: a disease entity. *Ann Intern Med* 1959; **51**:1253–7.
38. Reiman HA. Hepatitis: a feature of peritonitis. *JAMA* 1961; **178**:334–5.
39. Althausen TC, Deamer WC, Kerr WJ. The false acute abdomen. I Henoch's Schonlein purpura and abdominal allergy. *Ann Surg* 1937; **106**:242–51.
40. Armenian HK, Khachadurian AK. Familial paroxysmal polyserositis: clinical and laboratory findings in 120 cases. *Leb Med J* 1973; **26**:605–14.
41. Neequaye J, Jelly AE. Acute hepatitis in recurrent heriditary polyserositis (familial Mediterranean fever). *J Trop Pediatr* 1994; **40**:243–5.
42. Majeed HA, Halabi I, Al-Taleb O. Recurrent hyperbilirubinemia: a feature of familial Mediterranean fever: report of a child and review of the literature. *Ann Trop Pediatr* 1998; **18**:13–15.
43. Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, Gafni J. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. *N Engl J Med* 1974; **314**:1001–5.
44. Zemer D, Pras M, Sohar E, Modan M, Cabilli S, Gafni J. Colchicine in the prevention and treatment of amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986; **314**:1001–5.
45. Cattan R, Mamou H. 14 cas de Maladie periodique de dont 8 compliques de nephropathies. *Semaine Hop Paris* 1952; **28**:1062–70.
46. Saatci U, Ozen S, Ozdemir S, Bakkaloglu A, Besbas N, Topaloglu R, Arslan S. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. *Eur J Pediatr* 1997; **156**:619–23.
47. Bakir F, Mortada M. Periodic peritonitis: report of 41 cases without amyloidosis. *Trans Roy Soc Trop Med Hyg* 1975; **69**:111–17.
48. Gafni J, Ravid M, Sohar E. The role of amyloidosis in familial Mediterranean fever: a population study. *Isr J Med Sci* 1968; **4**:995–1002.
49. Eliakim M. Incidence of amyloidosis in recurrent polyscrositis (familial Mediterranean fever). *Isr J Med Sci* 1970; **6**:2–6.
50. Aivazian AA, Zavgorodniaia AM, Abramian MK, Pashenian CA, Bagdasrian GB, Guyumjian IO, Orsepian LA. Immunogenetics of periodic disease. *Klin Med* 1977; **55**:41–79.
51. Saatci U, Bakkaloglu A, Ozen S, Besbas N. Familial Mediterranean fever and amyloidosis in children. *Acta Paediatr* 1993; **81**:705–6.
52. Meyerhoff J. Familial Mediterranean fever: report of a large family, review of the literature and discussion of the frequency of amyloidosis. *Medicine* 1980; **59**:66–77.
53. Pras E, Langevitz P, Levneh A, Zemer D, Migdal A, Padeh S. Genotype–phenotype correlation in familial Mediterranean fever: a preliminary report. In: Sohar E, Gafni J, Pras M, eds. *Proceedings of the First International Conference on FMF*. London and Tel Aviv, Freund Publishing House, 1997:260–4.
54. Dagan T, Danon T, Lotan R, Magal N, Ogur G, Tokguz G, Schwabe A, Fischel Ghodsian N, Rotter JI, Schlezinger M, Shohat M. Phenotype-genotype correlation in familial Mediterranean fever. In: Sohar E, Gafni J, Pras M, eds. *Proceedings of the First International Conference on FMF*. London and Tel Aviv, Freund Publishing House, 1997:109–14.

55. Shohat M, Lotan R, Magal N, Ogur G, Tokguz G, Schwabe A, Fischel-Ghodsian N, Kastner D, Rotter JI, Schliezinger M, Daum T. Association between ancestral haplotype in the MEFV locus and FMF amyloidosis. In: Sohar E, Gafni J, Pras M, eds. *Proceedings of the First International Conference on FMF*. London and Tel Aviv, Freund Publishing House, 1997:115–19.

56. Said R, Hamzeh Y, Said S, Tarawneh M, Khateeb M. The spectrum of renal involvement in familial Mediterranean fever. *Kidney Int* 1992; **41**:414–19.

57. Grose C, Schnetzer JR, Ferrant A, Viadutiu AO. Children with hyperimmunoglobulinemia D and periodic fever syndrome. *Pediatr Infect Dis J* 1996; **15**:72–7.

58. Drenth JPH, Boom BW, Toonstra J, Van der Meer JWM. Cutaneous manifestations and histological findings in the hyperimmunoglobulinemia D syndrome. *Arch Dermatol* 1994; **130**:59–65.

59. Livneh A, Drenth JPH, Klasen IS, Langevitz P, Goerge J, Shelton D, Gummcio DL, Pras E, Kastner D, Pras M, Van der Meer JWM. Familial Mediterranean fever and hyperimmunoglobulinemia D syndrome: Two diseases with distinct clinical, serological and genetic features. *J Rheumatol* 1997; **24**:1558–63.

60. Drenth JPH, Mariman ECM, Saskia D, Van der Velde-Visser, Hans-Hilger Ropers, Van der Meer JWM. Location of the gene causing hyperimmunoglobulinemia D and periodic fever syndrome, differs from that for familial Mediterranean fever. *Hum Genet* 1994; **94**:616–20.

61. Eisenberg S, Askentijevich I, Deng Z, Kastner D, Matzner Y. Diagnosis of familial Mediterranean fever by a mollecular genetics method. *Ann Inter Med* 1998; **129**:539–42.