Familial Mediterranean fever in children: a single centre experience in Jordan

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حمى البحر المتوسط العائلية لدى الأطفال: خبرة مركز طبي وحيد في الأردن

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الخلاصة: تنتشر حمى البحر المتوسط إلى حد ما بين العرب. وقد قام الباحثان في إطار هذه الدراسة بمراجعة سجلات 56 من المرضى الذين شُخِّصت حالتهم بأنها حمى البحر المتوسط العائلية، ومتابعة حالتهم في مركز الملك حسين الطبي في الأردن على مدى أربع سنوات، للتعرُّف على مُرْتَسَماتهم السريرية، ومسار المرض، والنمط الجيني، والمعالجة، والمضاعفات. وشملت الدراسة 30 من الذكور، و26 من الإناث، وكان متوسط أعمارهم عند بدء الدراسة 5.2 عاماً. ولوحظ أن الآلام البطنية هي العرض الأكثر شيوعاً (79٪)، يليه التهاب المفاصل (13٪)، وآلام الصدر (4٪). ولوحظت سوابق إصابة بالمرض في العائلة لدى 50٪ من المرضى. وفي ما يتعلق بالمعالجة، لوحظت استجابة جيدة للكولشيسين لدى 97٪ من المرضى، ولم تسجَّل أي حالة للداء النشواني amyloid لدى المرضى بعد متابعة استمرت خمس سنوات. وكان النمط الجيني الأكثر شيوعاً هو M694 (64٪)، يليه النمط المتغاير الزيجوت M694V-V726A (23٪) ثم النمط E148Q (8٪).

ABSTRACT Familial Mediterranean fever is quite prevalent among Arabs. We reviewed the files of 56 patients diagnosed with familial Mediterranean fever and followed up at King Hussein Medical Centre in Jordan over 4 years for their clinical profile, course, genotype, treatment and complications. There were 30 males and 26 females with a mean age at onset of 5.2 years. Abdominal pain (79%) was the commonest manifestation, followed by arthritis (13%) and chest pain (4%). Family history was positive in 50% of patients. Regarding treatment, 97% of patients responded well to colchicine, and amyloidosis was not documented in any patients after 5 years follow-up. The commonest genotype was M694 (64%), followed by heterozygous M694V-V726A (23%) and E148Q (8%).

Fièvre méditerranéenne familiale chez l'enfant : expérience unicentrique en Jordanie

RÉSUMÉ La fièvre méditerranéenne familiale est assez répandue chez les Arabes. Nous avons examiné les dossiers de 56 patients ayant eu un diagnostic de fièvre méditerranéenne familiale et suivis au Centre médical Roi Hussein en Jordanie sur une période de 4 ans afin d'étudier leur profil clinique, l'évolution de la maladie, le génotype, le traitement et les complications. Il y avait 30 sujets de sexe masculin, 26 de sexe féminin et l'âge moyen à l'apparition de la maladie était 5,2 ans. Les douleurs abdominales (79 %) étaient la manifestation la plus courante, suivies par l'arthrite (13 %) et les douleurs thoraciques (4 %). Il y avait des antécédents familiaux positifs chez 50 % des patients. En ce qui concerne le traitement, 97 % des patients répondaient bien à la colchicine et une amyloïdose n'a été documentée chez aucun des patients après un suivi de 5 ans. Le génotype le plus courant était M694 (64 %), suivi par le génotype M694V-V726A hétérozygote (23 %) et E148Q (8 %).

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive familial paroxysmal polyserositis of unknown pathogenesis [*1*]. It is a multisystemic disease characterized mainly by painful attacks of sterile peritonitis, pleuritis, arthritis, or erysipelas-like erythema, usually accompanied by fever [*1*]. The disease is mostly prevalent in Arabs, Armenians, Turks and Sephardic Jews; however there are some differences in clinical manifestations among these ethnic groups [*2*]. The diagnosis of FMF requires a high index of suspicion and is based on the clinical criteria and family history, when available [*3*]. Until recently the only specific laboratory test for this disease was the documentation of C5a-inhibitor deficiency in serosal or synovial fluid and that requires invasive procedures [*4*]. The prognosis for patients with FMF is determined mainly by the presence or absence of amyloidosis; in its absence, life expectancy is normal [*5*]. Treatment with colchicine has greatly altered the prognosis by arresting amyloidosis even if it does not prevent febrile attacks [*6,7*].

The gene responsible for FMF is designated *MEFV* and was recently cloned [*8*]. Its protein product pyrin, or marenostrin, has been found to be homogenous with previously described nuclear factors that may play a role in the regulation of the inflammatory process [*9*]. Several mutations have been identified; one has been found in populations with a higher incidence of systemic amyloidosis, whereas another has been found in a population in which amyloidosis was less common [*6*].

In this paper we describe the clinical profile, course and complications of FMF in 56 patients attending one medical centre in Jordan. To the best of our knowledge this is the first report from King Hussein Medical Centre regarding FMF in children.

Methods

We reviewed the files of 56 patients with the diagnosis of FMF who were followed up in the paediatric immunology clinic at King Hussein Medical Centre from January 2000 to September 2004. King Hussein Medical Centre is the largest medical center in Jordan. It provides medical services to military personnel and their families. The paediatric rheumatology clinic was established in 2000. Along with 2 rheumatology clinics at the university hospitals in Amman and the north of Jordan, our clinic receives children referred with the suspicion or confirmed diagnosis of FMF who hold military health insurance. This insurance accounts for the second largest sector of medically insured individuals.

Patients were diagnosed with FMF if their manifestations were compatible with those of FMF, and if no alternative diagnosis could be found to explain their symptoms. Diagnosis of FMF was based on the criteria of Livneh et al. [*3*] (Table 1). Our study included children up to the age of 14 years. All patients whose files were complete were included in the study. The clinical profile, course, genotype, treatment and complications are presented.

Results

Of the 56 patients diagnosed with FMF, 30 (54%) were boys and 26 (46%) were girls. The age range was 1 to 14 years and all were Arabs. For 29 children, their illness had started before the age of 5 years; the mean age at onset was 5.2 years (Table 2). Abdominal pain was the commonest presentation; it was seen in 44 patients (79%), followed by arthritis (13%) and chest pain (4%). Only 1 patient presented with acute scrotal swelling, while none had episodic fever or myalgia as a presenting feature (Ta-

Table1 Clinical criteria for diagnosis of familial Mediterranean fever [3]

Criteria
Major criteria
1–4 typical attacks 1. Peritonitis (generalized) 2. Pleuritis(unilateral) or pericarditis 3. Monoarthritis (hip, knee, ankle) 4. Fever alone 5. Incomplete abdominal attacks
Minor criteria
1–2 incomplete attacks involving 1 or more of the following sites: Chest Joint Exertional leg pain
Favourable response to colchicine

The requirements for the diagnosis of FMF are ≥ 1 major criterion or ≥ 2 minor criteria.

ble 3). A positive family history was present in 27 (48%) patients; positive history was commoner in uncles, followed by siblings and less commonly in parents.

Abdominal pain was generalized in most of the patients. Few patients had suprapubic and either left or right fossae pain. The abdominal pain was severe and lasted for 1–3 days in most of our patients. Fever was not reported by the parents in almost one-third of the patients but was documented in hospital; the rest of the patients reported fever in most of the attacks. Fever ranged between 37.8 °C and 40.0 °C.

Table 2 Age at onset in 56 children with familial Mediterranean fever

Age (years)	No.	%
1–5	29	52
6–10	18	32
>10	9	16
Total	56	100

Table 3 Main presenting feature in 56 patients with familial Mediterranean fever

Main presenting feature	No.	%
Abdominal pain	44	79
Chest pain	2	4
Arthritis	7	13
Episodic fever	0	0
Myalgia	0	0
Angio-oedema	2	4
Scrotal swelling	1	2
Total	56	100

Arthritis was seen in 7 (13%) patients; 6 had monoarthritis and 1 had ankylosing spondylitis-like pain. Only large joints were involved, mostly the knees followed by the ankles. Other patterns of joint involvement were not seen. Most patients reported arthralgia of multiple joints during the attack. Chest pain was the initial presentation in only 2 (4%) patients, but 17 patients who presented initially with abdominal pain reported pleuritic chest pain later in the course of the disease, which was unilateral, without specific site predilection, and lasted a shorter time than abdominal pain (average 1–2 days). One of our patients had recurrent moderate pericardial effusion that responded to colchicine. Scrotal swelling was the initial presentation in 1 patient only, it was a painful swelling of the left side of the scrotum for 2 days, and appropriate clinical and radiological evaluation excluded torsion. There were 3 patients with cutaneous manifestations as the initial presentation; 2 of them had angio-oedema; the father of one of these patients had had similar episodes but laboratory tests excluded hereditary angioneurotic oedema and other acquired causes.

The third patient had Henoch–Schönlein purpura, while other skin lesions such as erysipelas-like erythema, maculopapular rash and urticaria were not reported.

Only 2 of our patients had undergone appendectomy. Other surgical procedures such as arthroscopy, synovectomy and scrotal exploration were not carried out. During the 5 years of follow-up, none of our patients was found to have amyloidosis; also this was not documented in other members of the family with a similar diagnosis. Laboratory results showed increase in erythrocyte sedimentation rate, C-reactive protein and white blood cell count 15 000–18 000/mm^3 during the attacks only. Two patients had persistent haematuria; they were found to have familial benign haematuria. Six (6) patients with arthritis had their joints aspirated, the result of which was consistent with inflammation with negative culture results.

Genotype studies were done for 26 patients: homozygous M694V was seen in 18 patients (69%); heterozygous M694V-V726A in 6 patients (23%); 2 (8%) patients had heterozygous E148Q.

Colchicine was prescribed to all patients (maximum total dose = 2 mg). The doses ranged between 0.5 mg and 2 mg daily according to age and response. Compliance was reported by families as good. The attacks disappeared completely in 68% of cases, a significant decrease in the number and severity of attacks was reported in 27%, and 3% showed no response to treatment. Those patients not responding failed to show alternative diagnosis after extensive study; however, when the total dosage was divided into 2–4 doses, they showed some improvement. Gastric upset after treatment was reported in 12 (21%) patients initially but it then subsided spontaneously. Mild hair loss was reported in 9 (16%) patients. One patient had severe diarrhoea and was found to have subtotal villous atrophy not consistent with coeliac disease; however these histological changes improved after stopping treatment, and diarrhoea did not recur with the gradual increase of the dose given every 6 hours.

Discussion

The prevalence of FMF in Jordan has been estimated to be 1:2600 with a gene frequency of 1:50 [*7,10*]. Our sample represents 11% of patients with FMF reported by other local centres in Jordan: 47% were females and 53% males with a ratio of 1:1. Majeed et al. found a slight preponderance in females in their cohort from Jordan [*1,10*]. Both our data and those of Majeed et al. do not support the suggestion that FMF may have incomplete penetrance [*11*].

Early recognition of FMF was suboptimal; the mean delay in diagnosis was 5.6 years in our patients; this is similar to the delay observed by other researchers [*10,11*]. This delay could be due to the low index of suspicion for the diagnosis, and the episodic nature of the disease with its expanded clinical profile at initial presentation. Recurrent generalized abdominal pain was the most common feature and the incidence and duration of pain was similar to that reported by Majeed et al. [*12*]. Even though chest pain has almost the same characteristics in all cohorts; the prevalence of pain as an initial presentation is variable [*12*]. Majeed et al. [*13*] reported 71 out of 476 patients with chest pain as the presenting feature, which is higher than our data, 4% of patients. Such a difference in figures could be explained by the fact that our cohort included only children up to the age of 14 years compared with others and such a condition can be under-reported in this age group because of difficulty in describing these symptoms in younger children.

Chest pain was followed abdominal pain in 70% of our patients; a similar observation has been reported by others [*12,13*]. The frequency of arthritis is variable among different ethnic groups: in our group it was 13%, while it has been reported higher in Jews, followed by Armenians, and less commonly in Turks [*12,13*]. The pattern of arthritis in our cohort was similar to others, where monoarthritis of large joints was the commonest presentation [*12,13*]. One of our patients had sacroiliitis, while other patterns such as juvenile rheumatoid arthritis-like or acute rheumatic fever-like were not seen in our patients. This differs from Majeed et al., who reported that 59 patients out of 199 had such patterns [*13*].

Recurrent episodic fever as the presenting features was not documented in any of our patients. The presentation with fever alone makes diagnosis difficult and all patients who had episodes of fever in our clinic and were referred with a provisional diagnosis of FMF were found on further investigation to have other conditions such as juvenile idiopathic arthritis (JIA), vasculitis and Behcet disease. Fever was reported less frequently by other researchers, the highest was 15 out of 476 patients reported by Majeed et al. [*13,14*]. Our patient who presented with acute painful scrotal swelling was a 4-year-old male who had a positive family history of FMF and responded well to colchicine. Exercise-induced myalgia was not reported in our group, while it has been documented in other studies [*15, 16*]. None of our patients had chronic renal disease complicating FMF and, more interesting, was the absence of such complications in other adult members of the families with FMF. Majeed et al. reported only 2 cases of renal disease in Jordan [*17*]. They were not on colchicine prophylaxis. Reports on different ethnic groups showed a variable incidence of renal disease even in the same ethnic group in the same country; it has been reported in 12%–42% of Jews, 0%–24% of Armenians and 7%–60% of Turks [*15,17*].

Recently genotype–phenotype correlations have started to emerge; the genotypic studies done on our patients showed homozygous M694V to be commonest, followed by heterozygous V726A. Similar results were reported by Majeed et al. among Arab patients [*18*]. In addition, 8% of our patients had the mutation E148Q which was also seen in 3.5% of symptomatic Turks as reported by Yilmaz et al. [*19*]. This same mutation has been reported to be the commonest mutation in Ashkenazi Jews, who generally have a milder disease [*20*].

Conclusion

Because this is the first report from King Hussein Medical Centre regarding FMF in children, it provides the expanded clinical profile of FMF in children at our centre and allows comparison with other reports from Jordan and the region. Our study focused on children up to the age of 14 years while other reports from Jordan included older ages. Another important aspect is that our study looked at the genotypic profile of our patients that can help to correlate with the phenotypic profile.

FMF is a clinical diagnosis with validated diagnostic criteria. It is quite prevalent in the Mediterranean region necessitating a high index of suspicion in patients from high-risk ethnic groups. Although significant progress has been made in our understanding of the disease and its genotypes, many patients are still not identified. Furthermore, a rapid, reliable, cost-effective test for detecting the common mutations is required to be applied at a wider level.

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