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The clinical patterns of arthritis in children with familial Mediterranean fever

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Summary

We studied the clinical patterns of arthritis in 133 children with familial Mediterranean fever (FMF) over 5.5 years. Six clinical patterns were noted. The commonest was recurrent monoarticular arthritis as seen in 95 children (71%), mainly affecting the knee and ankle joints. This type followed two different courses: acute (<1 month) and chronic (>1 month). In 18 (14%) children, both knee or ankle joints were simultaneously and symmetrically involved: here too the course was either acute or chronic. Five (4%) children developed symmetric polyarthritis similar to juvenile rheumatoid arthritis (JRA). Six (4%) children developed asymmetric oligoarticular arthritis similar to acute rheumatic fever (ARF). The small joints of the hands (SJH) were involved in seven (5%) children, and the small joints of the feet in one. One child developed sacroiliitis similar to ankylosing spondylitis (AS). Between attacks, the joints were normal. Overall, outcome was good: residual damage of the hip joint occurred in one patient and of the shoulder in another. Although the clinical presentation and course of FMF arthritis are diverse, delineating these clinical patterns may help with earlier recognition and treatment. The low incidence of residual articular damage in this study may be related to the use of colchicine prophylaxis.

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, pleuritis and arthritis.[3] Other areas less commonly affected are the skin,[4] the tunica vaginalis,[5] the pericardium[6] and the central nervous system.[7] It is inherited as an autosomal recessive gene, located on the short arm of chromosome 16.[8,9] The striking feature of the disease is that it affects certain ethnic groups disproportionately, mainly Arabs, Jews, Armenians and Turks.[2]

In the English literature, studies of FMF arthritis involve relatively small numbers of adult patients, and describe mainly the monoarticular type.[10] We have previously studied FMF arthritis in 44 children over 11 years; the arthritis was monoarticular in 80% and polyarticular in 20%.[11] More recently, we reported a high prevalence and gene frequency of FMF in Jordan.[12] The main aim of this study was to delineate the clinical patterns of arthritis seen in an additional group of 133 children with FMF arthritis.

Methods

From January 1991 to June 1996, 336 children with FMF were seen in the paediatric FMF clinics of the teaching hospitals of the Faculties of Medicine, Jordan University of Science and Technology, Irbid, North Jordan, and the University of Jordan, Amman, Jordan. The children were referred from primary health-care centres by their family physicians. Information was obtained from the parents in the presence of the child. The following tests were performed on all children: haemoglobin, white cell

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count, platelets, erythrocyte sedimentation rate, urine microscopy and culture, abdominal ultrasound, stool analysis and culture, Widal and brucella agglutination tests, kidney and liver function tests. Other investigations performed when necessary included haemoglobin electrophoresis, barium meal and follow-through, plain chest and bone radiographs, tests for antinuclear antibodies, anti-double-stranded-DNA antibodies, C3, C4 and CH50, hepatitis B surface antigen, rubella virus IgM antibodies, rheumatoid factor and antistreptolysin O titre and immunoglobulins.

Follow-up

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

Diagnostic criteria

Diagnosis of FMF was based on the criteria of Heller *et al.*[13]: (i) short attacks of fever recurring at varying intervals; (ii) pain in the abdomen, chest, joints or skin accompanying the fever; (iii) absence of any causative factor or pathological finding capable of explaining the clinical picture.

Results

Of 336 children with FMF, 133 (40%) developed arthritis, in 80 (24%) of whom arthritis was the presenting feature. This group of 133 was the subject of this study. Sixty-nine were boys and 64 were girls. Family history was positive in 75 (56%). Age at onset (Table 1) was 6 months to 17 years, mean 5.7 years. The majority developed arthritis aged <10 years. Arthrotomy was performed in 20 children.

Clinical patterns

Unlike peritoneal or pleuritic attacks, the synovial attack exhibits wide variation in clinical features (Table 2), duration and clinical course (Table 3), giving rise to diagnostic problems. However, we noted six distinct clinical patterns, namely monoarticular (acute and chronic), bilateral symmetric two-joint arthritis (acute and chronic), polyarticular symmetric arthritis similar to JRA, oligoarticular asymmetric arthritis similar to ARF, recurrent arthitis involving the SJH, and a pattern involving the sacroiliac joints resembling AS.

Table 1 Age at onset in children with FMF arthritis and those with FMF

Age (years)	No. with FMF arthritis (%)	No. with FMF (%)
<2	14 (11)	73 (22)
2–5	50 (37)	115 (34)
6–10	51 (38)	104 (31)
>10	18 (14)	44 (13)
Total	133 (100)	336 (100)

Monoarticular

The most common pattern was recurrent monoarticular arthritis of the same joint (knee or ankle) throughout the course of the disease. In recurrences, the same joint was involved in a similar fashion. A second pattern was monoarticular arthritis alternating between the right and left knee or right and left ankle. A third pattern was monoarticular arthritis alternating between the knee and ankle. The wrist, elbow and shoulder joints were involved in one patient each, alternating with the knee or ankle (Table 2).

The usual presenting feature was moderate pain in a large joint, with or without fever and usually associated with a large effusion, particularly in the knee. Redness over the joint was occasionally noted. Pain, hotness, tenderness and severe limitation of movement were severe for the first day, but tended to decrease quickly over a few days. The subsequent course was either acute or chronic. In the acute form (the most common), arthritis subsided and the joint was usually normal in one week, rarely in 2–3 weeks. In the chronic form (>1 month) pain, hotness, tenderness and limitation of movement disappeared similarly in a few days to one week, but the swelling lasted for a few months to a few years (Table 3). However, the outcome of the chronic form was good, except in two patients where swelling and mild-to-moderate limitation of movement persisted, leaving some functional incapacity of the hip in one patient and the shoulder in another. Of these two patients, one had no colchicine prophylaxis, and the other was irregularly compliant with the prophylaxis.

Simultaneous symmetric two-joint arthritis

This began as simultaneous bilateral symmetric arthritis of either both knees (9 patients), both ankles (5 patients) or alternating between knees and ankles (4 patients). The fever was mild, and the tenderness and limitation of movements were minimal and lasted for a few days to one week. The subsequent course was either acute or chronic. In the acute form (12 patients), the arthritis subsided in about one week. In the chronic form (5 patients), the swelling lasted for 6–12 weeks, and in one patient the swelling lasted for 6 months. In four patients, this

Table 2 The clinical patterns of FMF arthritis

Pattern	Joints affected	No. of patients
Monoarticular	Knee*	55
	Ankle**	36
	Elbow**	2
	Shoulder**	1
	Wrist**	1
		Subtotal 95 (71%)
Simultaneous symmetric two-joint arthritis	Both knees	9
	Both ankles	5
	Alternating	4
		Subtotal 18 (14%)
Polyarticular symmetric	JRA-like	5 (4%)
Oligoarticular asymmetric	ARF-like	6 (4%)
SI joint involvement	AS-like	1 (1%)
Small joints of the hands		7 (5%)
Small joints of the feed		1 (1%)
Total		133 (100%)

*May be alternating; **Alternating with knee or ankle joints. JRA, juvenile rheumatoid arthritis; ARF, acute rheumatic fever; SI, sacroiliac joints; AS, ankylosing spondylitis.

Table 3 Duration of FMF arthritis

Pattern	1 week	6–12 weeks	3–6 months	6–12 months	>1 year
Monoarticular	76	6	8	1	4
Simulataneous symmetric two-joint arthritis	12	5	1		
Polyarticular symmetric (JRA-like)		5			
Oligoarticular asymmetric (ARF-like)		6			
SI joints (AS-like)			1		
Small joints of hands	6	1			
Small joints of the feet	1				

JRA, juvenile rheumatoid arthritis; ARF, acute rheumatic fever; SI, sacroiliac; AS, ankylosing spondylitis.

pattern of arthritis alternated with monoarticular arthritis of the knee or ankle joints. All joints returned to normal.

Polyarticular symmetric arthritis

Three patients presented with a JRA-like severe aggressive systemic onset, and two as polyarticular with a less aggressive clinical course. The joints returned to normal in 6–12 weeks. Three girls (ages at onset 3, 8 and 10 years) presented with systemic-onset JRA with high fever, and polyarticular symmetrical arthritis including the SJH; the cervical spine was involved in two, with marked neck stiffness. The fever pursued a course of recurrent paroxysmal episodes, each lasting 2–3 days, with recurrences over a period of 4 weeks. Two had a family history of FMF, and one had alternating recurrent abdominal and chest pain. All had a high ESR of 80–120 mm in the first hour. The following tests were negative: ANA, RF, C3, C4, anti-ds-DNA antibodies, ASOT, blood and throat culture, brucella agglutination test, HBsAg and rubella IgM antibody (rubella IgG antibodies were positive). There was a modest response to ipobrufen, and joints returned to normal in 6–12 weeks.

Case history: patient 1

YA presented aged 3 years with recurrent attacks of high fever and polyarticular symmetric arthritis, each lasting for 'a few weeks to a few months' and a frequency of once every 6–18 months. Between attacks, the joints were reportedly normal. She was treated as systemic-onset JRA for 12 years. She never had colchicine prophylaxis. She presented to us aged 16, with high fever and polyarticular symmetric arthritis involving the cervical spine, shoulder, elbow,

wrist, knee and ankle joints. She never had recurrent abdominal or chest pain, the family history for FMF was positive. Apart from a high ESR (80 mm/1st h) investigations were normal. She was put on ipobrufen and colchicine. Fever settled in 3 days, and joints were normal in 8 weeks, except the left shoulder joint, which was left with limited movement. At the age of 17 years, she presented to us with a similar picture, and the response to oral prednisone 15 mg four times daily was dramatic. Fever settled in 24 h, she could walk on the fourth day, and the joints were normal in 10 days, except the left shoulder joint. Steroids could be tapered and stopped in 4 weeks.

Case history: patient 2

MA presented to us aged 10 years, with a 24 h history of high fever and polyarticular symmetrical arthritis including the SJH and the cervical spine with marked neck stiffness. Temperature was 39.5 °C and the joints were swollen, very tender, with severe limitation of movements and inability to stand or walk. She was hospitalized for a similar episode 18 months earlier. She was treated, and the joints normalized in 6 weeks. A past or family history of FMF was denied. The ESR was 120 mm/1st h, and other investigations were normal. A diagnosis of systemic-onset JRA was made, she was hospitalized and started on intravenous hydrocortisone 100 mg/6 h and diclofinac orally. Her temperature settled in 24 h, she could walk on the third day, and the joints normalized in one week. The dramatic response and rapid normalization of joints raised doubts about the diagnosis, and questioning of the girl and her mother revealed a past history of recurrent abdominal and chest pain and a positive family history of FMF. Steroids could be stopped in 4 weeks and she was started on colchicine prophylaxis 1.5 mg daily. In spite of this she developed two similar attacks over the next 2 years; they were milder and the response to oral prednisone was also dramatic.

Two other patients presented with recurrent episodes of mild fever of few days duration and polyarticular symmetric arthritis. Pain was moderate in the first 48 h and arthritis subsided in 6–12 weeks. One had history of recurrent abdominal pain and another had recurrent chest pain and a positive family history of FMF. The clinical course was not as aggressive as it was in the three girls. In spite of colchicine prophylaxis, milder recurrences occurred; the arthritis was polyarticular and generally symmetric, but was asymmetric in one child during a recurrence.

Oligoarticular asymmetric arthritis

Six patients developed this migratory pattern of arthritis lasting for 3–8 weeks. All of them had recurrent abdominal or chest pain and family history of FMF was positive in 4.

Case history

FS presented aged 11 with fever (38.5°C), swelling, hotness, pain, tenderness and limitation of movement of his right knee of 24 h duration. One month earlier he had developed fever and severe abdominal pain for 2 days; he escaped appendectomy. There was no recent history of sore throat, diarrhoea or urethritis, but he had had a similar episode of arthritis one year before. He was diagnosed with ARF, and maintained on monthly benzathine penicillin prophylaxis. His 5-year-old brother and 18-year-old uncle had recurrent abdominal pain; both had had appendectomies. The ESR was 60 mm/1st h, and other investigations were normal including ASOT, chest film, ECG and echocardiogram. He was put on aspirin 80 mg/kg/day, and the right knee arthritis subsided in one week. A few days later, he developed left ankle arthritis with no fever, followed after a few more days (still on aspirin) by arthritis of the right wrist; both joints normalized in a few days each. Benzathine penicilin was stopped and he was started on colchicine prophylaxis. Over a follow-up of one year, he developed no recurrences of abdominal or joint pain.

Sacroiliac joint involvement

One child developed arthritis of the sacroiliac joints.

Case history

SM presented elsewhere with fever and severe abdominal pain aged 10 months; laparatomy was performed. He remained well until a few years later, when he developed recurrent alternating abdominal and chest pain. He presented to us aged 14 years with arthralgia of both knees and lower-back pain of 4 months duration. There was no family history of FMF. The ESR was 35 mm/1st h and WBC 12000/mm. Radiographs of the SI joints showed widening of the joint spaces, suggesting an effusion. He was started on colchicine and diclofinac. Over a follow-up of one year, he developed no further episodes of abdominal or chest pain. However, the improvement of his back pain was only moderate. He was lost to further follow-up.

Small joints of the hands

Involvement of the SJH was seen in seven patients (Table 2). The fever was mild, and arthritis involved the metacarpophalyngeal and proximal interphalyngeal joints. There was pain, tenderness, and limitation of movement for 2 days, associated with mild oedema of the hands. Arthritis resolved in a few

days in six patients and in 6 weeks in one. All patients had recurrent abdominal pain and a positive family history of FMF. In two, arthritis of the SJH alternated with monoarthritis of the right knee and (in one) the left ankle. Colchicine prophylaxis was effective in preventing recurrent abdominal pain. However, similar but milder recurrences of arthritis of the SJH occurred showing the same pattern.

Recurrent arthritis of small joints of the feet was seen in one patient, who alternated this pattern of arthritis with recurrent abdominal pain.

Discussion

Arthritis is a cardinal and common feature of FMF.[10] The incidence in the present study was 40%. The incidence amongst Jewish children (75%) and adults (74%) (Table 4) was significantly higher than that reported in Arabs, Turks and Armenians:[2,3,11,14,16,25] the reason for this is unclear. However, this could be due to under-reporting; in our experience, the Jordanian medical profession is not fully aware of the high prevalence of this disease in Jordan. Arthritis can be the presenting feature of FMF. In the present study of 336 children, 80 (24%) children presented with arthritis, compared to 54(16%) of the 334 Jewish children with FMF reported by Zemer *et al.*[16]

The male/female ratio in our children with FMF ($n=336$) was 142/194 (0.7), but that of the subgroup with arthritis ($n=133$) was 69/64 (1.07). This suggests that boys with FMF are more at risk of developing arthritis.

The peak incidence of arthritis (75%) occured in children aged 2–10 years (Table 1). Although 22% of children with FMF presented aged <2 years, only 11% of children with FMF arthritis presented below this age group. This may indicate that FMF arthritis is not common under this age.

FMF arthritis has mainly been studied in adults by the pioneering works of Heller *et al.*[10] and Siguier *et al.*[17] Heller *et al.* described mainly two patterns of arthritis: the 'short attack' lasting for a few days and the 'protracted attack' lasting for more than one month. Siguier *et al.* described two main patterns: 'inflammatory monoarthritis' (like the 'short attack' of Heller *et al.*) and acute polyarthritis resembling Bouillaud's disease (akin to JRA), lasting 6–12 weeks. Both described arthralgia as a third pattern named 'abortive attack' by Heller *et al.* and 'simple arthralgia' by Siguier *et al.* In our experience, arthralgia is common amongst patients with FMF. However, it is subjective and non-specific, especially in children, making it difficult to delineate.

Familial Mediterranean fever is common in Jordan.[12] Observations from the present study involving 133 children with FMF arthritis seen and followed-up over 5.5 years, provided us with an opportunity to delineate six clinical patterns of FMF arthritis in childhood (Tables 2 and 3): recurrent monoarticular arthritis (parallel to the short and protracted forms of Heller *et al.* and the inflammatory monoarthritis of Siguier *et al.*); acute and chronic simultaneous symmetric two-joint arthritis; polyarticular symmetric arthritis resembling JRA (the 'acute polyarthritis resembling Bouillaud's disease' of Siguier *et al.*); oligoarticular asymmetric arthritis resembling ARF; recurrent arthritis of the SJH; and sacroiliac joint involvement resembling AS.

The acute and chronic forms of monoarticular arthritis in adults have been well described (under other names) in many reports including Heller *et al.*[10] and Siguier *et al.*[17] They do not seem to be different in children, as reported by us earlier.[11] The most characteristic features of the acute form of this subsyndrome are the sudden onset of arthritis in a large joint, characterized by a prominent effusion and the remarkable subsidence of arthritis in few days. Between the recurrent attacks, the joint is anatomically and functionally normal. The contrast between a patient in pain with prominent joint effusion in the first day, and the subsidence after a few days is dramatic and distinctive. In the first day of the first attack, septic arthritis or osteomyelitis should be ruled out. Similarly, brucellosis should be ruled out in areas where the disease is still prevalent. In recurrent attacks involving the same joint or

Table 4 Incidence of FMF arthritis in different series

Author (year)	Reference	*n*	Main age group	Ethnic group	No. with arthritis (%)
Sohar *et al.* (1967)	3	470	Adults	Jews	346 (74)
Schwabe and Peters (1974)	25	100	Adults	Armenians	37 (37)
Barakat *et al.* (1986)	2	175	Adults and children	Arabs	59 (34)
Ozdemir and Sokemen (1969)	14	57	Adults	Turks	25 (44)
Zemer *et al.* (1991)	16	334	Children	Jews	251 (75)
Majeed and Barakat (1989)	11	88	Children	Arabs	44 (50)
Present study	–	336	Children	Arabs	133 (40)

alternating with another joint, the diagnosis, in our experience, can confidently be made, even in the absence of a past history of other clinical features of serositis. Of the 95 patients with monoarticular arthritis, 19 (20%) developed the chronic form where the swelling lasted from 6 weeks to more than one year. Of the 34 patients described by Heller *et al.*, nine (27%) developed chronic monoarticular arthritis; the swelling lasted 3–8 months. Of 19 patients with chronic monoarticular arthritis in the present study, two (11%) developed articular damage (one hip and one shoulder), compared to five (56%) of the nine patients in Heller *et al.* developed articular damage.[10] Similarly of the 84 joints with chronic monoarticular arthritis seen in 57 patients, reported by Sneh *et al.*,[18] 27 joints (32%) developed articular damage, of which 21 (78%) were hip joints. Sneh *et al.* suggested that this poor prognosis of the hip could be due to attenuation of the arterial blood supply at the femoral head by synovial exudation. Early aspiration was suggested to prevent the complication of aseptic necrosis of the head of the femur. The low incidence (11%) of articular damage in our patients with chronic monoarticular arthritis, is striking. This is probably because the earlier studies were reported in 1966[10] and 1977[18] when colchicine prophylaxis was not available.

Eighteen (14%) patients developed simultaneous symmetric two-joint arthritis (Table 2); either both knees or both ankles. There was a tendency for knees and ankles to alternate in the course of the disease. Fever was mild or absent, and the arthritis was characterized by prominent effusion, clearly seen in the knees, and mild pain and tenderness for few days. Of the 18 patients, 12 had an acute course (<1 week) and six developed a chronic form where the swelling (without fever, pain or tenderness) lasted from 6 weeks to 6 months. There was no residual articular damage. In Heller *et al.*,[10] simultaneous involvement of two joints was 'rare'; however, there was no information about the number of patients, course of arthritis, joints involved or prognosis. In an earlier report, we described four children with bilateral symmetric arthritis of both ankles lasting 6 weeks.[11] We have not encountered such a recurrent pattern in other diseases. We believe this to be a distinct clinical subsyndrome of FMF arthritis which has not been described before. The diagnosis can be made in the first attack in the presence of past history of other features of serositis, and should be seriously considered if there is a family history of FMF. Once the arthritis shows its recurrent nature, this pattern can be readily recognized. Five (4%) patients developed polyarticular symmetric arthritis. The clinical course was similar to JRA (Tables 2, 3), and lasted 6–12 weeks. The clinical course in three patients was similar to systemic-onset JRA. The main difference was the fever, which was not continuous, but showed a paroxysmal episodic course. The characteristic salmon-red, evanescent rash accompanying the fever in the systemic-onset JRA, was also not seen, and joint recovery was much more rapid. Patients with either disease may develop serositis. However, recurrences in the course of FMF are far more frequent. The duration and severity of the episodes in FMF are characteristic. A positive FMF family history in a child with JRA is suspicious. The dramatic response to steroids (see case histories) in this pattern was not seen in our patients with JRA.[19] The prognoses of the two diseases are also quite different. FMF JRA-like arthritis lasts for 6–12 weeks with total recovery of the joints, whereas systemic-onset JRA is well known for its chronicity and joint destruction. The clinical course in the other two children was similar to the seronegative polyarticular onstype JRA; the fever was low-grade, and arthritis was mild to moderate in severity and lasted 6–8 weeks. This subsyndrome was recognized by Siguier *et al.* as the Bouillaud's-like form (parallel to JRA)[17] and one child was reported by us earlier.[11] However, this is the first report in English describing a group of children with this pattern in detail.

Six (4%) of our patients developed a clinical course of arthritis dominated by a migratory or additive pattern (see case history), lasting 6–12 weeks (Tables 2 and 3). The main feature of this pattern of FMF arthritis was, as in ARF, that a new joint was involved before the resolution of arthritis in the first joint. The fever was low grade and arthritis was oligoarticular and asymmetric. The joints involved were mainly the knee, elbow, ankle, wrist and shoulder joints. The cervical spine and SJH were spared. Three children with a similar clinical course were reported by us earlier,[11] and in the report of Heller *et al.*, 'arthritis sometimes developed in another joint before the resolution of an attack in the first'. The rheumatic arthritis is characterized by minimal swelling and severe pain, and in the absence of carditis, lasts 3–6 weeks.[20] In three of our patients with this pattern, the swelling, especially the knee, was greater than expected in rheumatic arthritis. Recurrences occur in both diseases, and it may be tempting to monitor for signs of carditis in subsequent recurrences to strengthen the diagnosis of ARF. However, if the patient escapes carditis in the initial attack, they continue to do so in subsequent recurrences.[21–23] Recurrences in rheumatic children on benzathine penicillin G secondary prophylaxis are rare.[23] In the child diagnosed as ARF, recurrences while on secondary prophylaxis should raise suspicion of FMF, especially in the presence of a positive family history.

In contrast to the experience of Heller *et al.*, where 'involvement of the metacarpophalangeal and interphalangeal joints of the hands was most

unusual',[10] seven of our patients developed arthritis of the SJH (Tables 2 and 3).

One of our patients developed lower-back pain and radiological evidence of sacroiliitis. The patient was lost to follow-up after one year. A similar child was reported by us earlier.[11] The involvement of the sacroiliac joints in the course of FMF is now well recognized in children and adults. Lehman *et al.* reported two Armenian children with FMF who developed sacroiliitis.[24] Shahin *et al.* reported one instance of sacroiliitis in a series of 40 patients with FMF,[25] and Heller *et al.* described sacroiliitis in 3/34 patients; one developed iridocyclitis and was probably true ankylosing spondylitis.[10] In the report by Bridet and Wolff, of 43 patients, six (14%) developed radiological changes in the sacroiliac joints; these changes were noted despite the absense of clinically symptomatic joint disease.[26] The low incidence of sacroiliitis in the present study is probably an underestimation, as radiology of the sacroiliac joints was not routinely performed in our patients. The sacroliitis of FMF is not HLA-B27-associated.[11,24]

Data from this study, taken with those of Heller *et al.*,[10] Siguier *et al.*,[17] and our previous report,[11] delineate six distinct clinical subsyndromes of FMF arthritis. Arthritis of FMF is a distinct clinical entity, and some types, mainly the recurrent monoarticular and the recurrent simultaneous symmetric two-joint arthritis, have highly distinctive patterns.

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