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ABSTRACT
Juvenile Idiopathic Arthritis (JIA) and Familial Mediterranean Fever (FMF) may involve the same population of children and be confused at times. In a cohort of 350 consecutive FMF patients followed by us, 98 had onset before 10 years of age and, of those, JIA was present in 3. All three had the M694V mutation of the MEFV gene and were of North African ancestry. The prognosis of these 3 was extremely poor: one developed bilateral knee osteonecrosis with total joint replacement, repeated ileal obstruction with small bowel resection, renal failure and sterility due to amyloidosis and osteoporotic fractures and died at 42 years of age; a second developed deforming erosive arthropathy and underwent bilateral total hip replacement; the third developed severe erosive polyarthritis and also underwent bilateral hip replacements. Aggressive treatment is indicated when JIA and FMF coexist.

Introduction
Familial Mediterranean Fever (FMF) is a genetic disease with autosomal recessive transmission, occurring mainly in Sephardic Jews, Armenians, Turks, Arabs and druze with a gene carrier frequency reaching 1:10 in some affected populations (1-3). Attacks of fever, accompanied by abdominal, chest or joint pain and the gradual development of nephropathic amyloidosis of the AA type (1, 4) characterize the disease. Less common manifestations include erysipelas-like erythema, acute scrotal attacks, febrile myalgia and chronic arthritis (1, 4, 5). Colchicine in a dose of 1 to 2 mg/day prevents the febrile attacks in most patients and amyloidosis in all (6, 7).

Recently the gene associated with FMF has been cloned (8, 9) and 30 disease-associated mutations identified. The protein encoded by this gene has been named pyrin/marenostrin. The wild type protein is believed to function as a direct downregulator of inflammation, specifically in neutrophils. It would appear that the function of the mutated pyrin/marenostrin protein is impaired in terms of controlling inflammation in FMF alone or in FMF associated with other inflammatory diseases such as Behçet’s, polyarteritis nodosa or asthma (10-13). Juvenile idiopathic arthritis (JIA) is the most common chronic arthritidic condition of children (14). JIA is a general term encompassing disease which begins before the age of 16 years and which is characterized primarily by arthritis that persists for at least 6 weeks. The systemic subgroup of JIA with arthritis, high fever, rash and serositis may be confused at times with FMF.

Over the years we have treated pediatric patients who had both FMF and JIA. The aim of the present study was to determine the prevalence of JIA in our FMF population and to describe the clinical, demographic and genetic features, as well as prognosis of the disease combination. The clinical diagnosis of FMF was based on the internationally accepted criteria reported by Livneh (15). A cohort of 350 consecutive FMF patients was screened. Of these, 98 were patients diagnosed with FMF in childhood (onset before 10 years of age). From this latter group, those with JIA (onset before 16 years of age) were eligible for inclusion in the study. Charts were reviewed for clinical data, including disease activity. We report here 3 cases of FMF associated with JIA. A 58-year-old male patient with FMF onset at the age of 11, who developed chronic arthritis of the hip at the age of 32, was not included.

Case reports
Case 1
A 3-year-old male child, born in Israel
to parents of Moroccan origin, was diagnosed with FMF after recurrent short attacks of fever, abdominal pain, and synovitis of knees with a high erythrocyte sedimentation rate (ESR) of 62 mm/hour. FMF was suspected in the grandfather. In the pre-colchicine era, the patient was treated with dietary fat reduction. At the age of 8, the child experienced protracted arthritis of the ankles, hands and feet with morning stiffness, persistent anemia, high ESR (80 mm/hr) and a negative Rose-Waaler reaction. The clinical picture was suggestive of JIA and the patient was treated with salicylates and glucocorticoids.

At the age of 12, he was hospitalized for recurrent abdominal pain with fever, and synovitis of both hands, knees, ankles and feet was noted. JIA associated with FMF was diagnosed. He was treated with colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), parenteral gold salts and glucocorticoids. On repeat testing, rheumatoid factor (RF) and antinuclear antibody (ANA) were negative. X-rays demonstrated erosions in both hands (Fig. 1) and feet. He developed bilateral osteonecrosis of knees at the age of 31 and subsequently underwent bilateral knee replacement.

Extra-articular complications ensued: repeated occurrences (8 episodes) of ileal obstruction were followed by several laparotomies and resection of the small bowel; continuous prophylactic colchicine therapy 1 mg/day did not prevent renal failure (urea 110 mg/dl, creatinine 2.9 mg/dl, proteinuria 1.9 gm/24h); on evaluation for sterility, a testicular biopsy revealed amyloid deposits (Fig. 2); prolonged therapy with glucocorticoids led to osteoporosis with vertebral compression and right humerus fractures. The patient was homozygous for the M694V mutation of the pyrin/marenostrin protein. He was treated with colchicine 1 mg/day, prednisone 10 mg/day, methotrexate 7.5 mg/week, alendronate 10 mg/day, calcium and vitamin D supplementation. At the age of 42, he died after ileal obstruction, with peritonitis, sepsis and renal failure.

Case 2
A 7-year-old girl, born in Israel to parents native to Morocco, presented with recurrent febrile attacks of abdominal pain every 8-12 weeks, which had started 4 years earlier. One brother has FMF. She showed a favorable response to colchicine 1 mg/day. At the age of 15, she complained of persistent pain in the hands, wrists, and knees symmetrically, with 2 hours of morning stiffness. The neck and hips became involved one year later. Persistent normochromic normocytic anemia was present, hemoglobin 11.4 g/dl, with an elevated ESR (80 mm/hr); ANA and RF were negative. Subsequent to this polyarticular JIA onset she developed swan-neck deformity.
mities with erosive subluxation of the hands and ulnar deviation, fusion of the C2–C3, C4-C5 vertebra (Fig.3) and end-stage damage of the hip joints. She was treated with NSAIDs, prednisolone <10 mg/day, continuous colchicine, auranofin, hydroxychloroquine and sulfasalazine. At the age of 25, she underwent right total hip replacement. At the age of 30, left total hip replacement was performed. The patient declines other DMARD therapy at the present time. She is homozygous for the M694V mutation of the pyrin/marenostrin protein.

Case 3
A 1-year-old girl, born in France to parents native to Tunisia, with several relatives with FMF, was hospitalized for fever and persistent monoarthritis of the right knee. A synovial biopsy revealed non-specific synovitis while culture was negative. She had recurrent episodes of fever, abdominal pain and arthritis. At age 6 prolonged glucocorticoid therapy was initiated. Recurrent febrile pleuritic, abdominal and joint pain attacks were treated with indomethacin and glucocorticoids. At the age of 11 she was diagnosed with FMF and colchicine was initiated but with uneven compliance. At the age of 16 she complained of persistent pain and swelling in both hands, feet, shoulders and knees with morning stiffness. Synovitis was noted. ESR was 48 mm/hour and C-reactive protein 20 mg/dl (normal <5 mg/dl). She was diagnosed to have FMF associated with JIA. The frequency of the febrile abdominal pain attacks decreased with colchicine 1 mg/d, but did not completely disappear. Higher doses were followed by severe diarrhea. The patient developed bilateral osteonecrosis of the femoral heads and underwent replacement of both hip joints at age 32 and 33. At this time, she has a severe erosive polyarthritis of the hands and feet, and persistent proteinuria at 500 mg/24 hours suggests amyloidosis. She is being treated with sulfasalazine and continuous colchicine. A genetic study for MEFV gene mutations revealed that this patient is homozygous for the M694V mutation.

Discussion
The clinical manifestations of JIA in children – including fever, serositis, adenopathy, splenomegaly, arthritis and rash in the systemic subtype – may be confused at times with FMF. The diagnostic confusion may be accentuated in FMF patients with protracted arthritis. Although most of the arthritis attacks resolve within a few weeks, about 10% of patients with FMF develop protracted arthritis persisting for months. Currently there are no established criteria for the definition or differential diagnosis of arthritis associated with FMF. Erosive symmetric lesions of both feet and hands with ulnar deviation, to the best of our knowledge, have been described only in JIA but not in FMF. The clinical patterns of arthritis in children with FMF were reported by Ma-jeed and Rawashded (16) who described 7 patients (5%) among 133 FMF children, with the small joints of the hands and one small joint of the feet involved. This JIA-like polyarticular disease returned to normal in 6-12 weeks with no erosions or permanent ulnar deviation described. Similarly, cervical fusion of C2-C4 apophyseal joints is generally not found in FMF, but has been well described in JIA. We found just one case report describing a patient with severe FMF complicated with amyloidosis with cervical spine involvement and cervical apophyseal joint fusion (C3-C7), with calcifications at the anterior longitudinal liga-ment, mainly at C5-6 (17). This case report differs significantly from our case described here, with late onset of the cervical X ray changes at the age of 39 while in our case the cervical fusion was seen at the age of 16. Recently, cervical spine disorders were studied in patients with rheumatoid arthritis and amyloidosis (18), with 111 of 147 (76%) patients found to have subluxation, impaction and apophyseal joint ankylosis. At this time, our patient with cervical spine involvement has no findings of amyloidosis. These radiologic features noted above, which are characteristic of JIA and not reported in FMF, helped to clarify the confusion between JIA and protracted arthritis of FMF in our cases.

In our population of childhood-onset FMF, we found 3 patients suffering from FMF associated with JIA (3.1%). Though our study included only a small group of patients, its findings suggest that this association has a poor prognosis. The articular involvement in this group appears to be very destruc-
tive: the 3 patients have erosive joint disease. All of them underwent bilateral hip or knee replacement in their early thirties. Their extra-articular manifestations are impressive with amyloidosis in 2 cases; one suffered chronic renal failure and recurrent ileal obstructions that required several abdominal operations and led to mortality when the patient was in his forties.

The severity of the association of both diseases has had a notable impact on the familial and social relations of these patients: one, at age 30, is unmarried; one is divorced; and the male patient, due to amyloidosis of the testis, suffered from infertility before his death.

It is interesting to note that our 3 patients are of North African ancestry and are homozygous for the MEFV, specifically the M694V mutation, which is known to be associated with a high prevalence of renal amyloidosis (19-20) and more severe articular and musculoskeletal manifestations (21).

A review of the medical literature from 1968 to 2002 using the MEDLINE database with the key words "familial Mediterranean fever" and "juvenile chronic arthritis" "juvenile rheumatoid arthritis" or "juvenile idiopathic arthritis" was performed. Particular attention was given to large series of children with FMF living around the Mediterranean basin in different countries: Israel (21,25), Jordan (16), Turkey (22,23), and Kuwait (24). These studies report the prevalence and the clinical patterns of arthritis in children with FMF, but did not specifically address or diagnose FMF associated with JIA. Protracted arthritis is relatively uncommon in childhood FMF and Majeed and Rawashdeh (16) offered the hypothesis that the low incidence of residual articular damage in children was related to the use of colchicine therapy.

The results of our study on a small number of patients suggest the importance of molecular genetic testing for familial Mediterranean fever in children in ethnic groups of Mediterranean origin suffering from juvenile idiopathic arthritis who are poorly responsive to therapy. A recent preliminary study that explored the significance of the MEFV gene in the expression of rheumatoid arthritis, an autoimmune, inflammatory, polygenic disease, reported that patients carrying one common MEFV mutation may present with more severe seropositive RA (26). The severe prognosis of JIA associated with FMF should motivate clinicians to initiate aggressive therapy early on, combining methotrexate with colchicines early on in those with the twin diseases and rapidly adding anti-TNF therapy if the patient does not achieve a rapid remission (27,28). Attention to this disease combination in a larger patient series would seem warranted.

References