

Recurrent Synovitis of Hip and *MEFV* Gene Related Arthritis in Children

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Research article

Keywords: FMF, MEFV gene, Recurrent synovitis of hip in children

Posted Date: December 19th, 2019

DOI: <https://doi.org/10.21203/rs.2.19267/v1>

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Abstract

Background: Familial Mediterranean fever (FMF) is an autosomal recessive inherited auto inflammatory disorder. Arthritis is the presenting finding of FMF in some patients, and sometimes it remains as the major manifestation of the disorder. This study reports three non-FMF patients with heterozygous MEFV gene mutations and an extraordinary arthritis as a recurrent synovitis of hip (RSH)

Methods: During 16-years from 2003 to 2019 at pediatric rheumatologic clinic among 195 recorded files, 3 patients with diagnosis of recurrent synovitis of hip (RSH) were reviewed thoroughly. Peripheral blood was collected from patients and the samples were screened for the 12 common MEFV gene pathogenic variants.

Results: This study included three patients, two female and one male with relapsing arthritis that has been located on hip joints as a sole manifestation and pathologic findings of MEFV mutations as follow: A744S, V726A, and R761H.

Conclusion: On the basis of possible role of MEFV gene in different rheumatic disease RSH could be considered as a MEFV gene related arthritis.

Key words: FMF, MEFV gene, Recurrent synovitis of hip in children

Background

Familial Mediterranean fever (FMF) is an autosomal recessive inherited auto inflammatory disorder. It affecting mainly Mediterranean people especially Jews, Armenians, Arabs, and Turks, however; it is now being recognized in non-Mediterranean populations, including Iranian, Italians and Greeks.

The clinical manifestations of FMF are characterized by recurrent periods of fever, associated with serositis, erysipelas-like erythema and arthritis. (1)

A gene for FMF (MEFV) has been identified on the short arm of chromosome 16, and more than 330 mutations in this gene have been demonstrated in patients with FMF (2).

Arthritis is the presenting finding of FMF in some patients, and sometimes it remains as the major manifestation of the disorder. (3)

The frequency of arthritis in FMF has been reported to range 40% and or more in different ethnic groups (4). The most common type of arthritis is large joints self-limited, recurrent, and short lived acute inflammation of the lower extremities. (3)

This study reports three non-FMF patients with heterozygous MEFV mutations and an extraordinary arthritis as a recurrent synovitis of hip (RSH), that is not typical for FMF and known rheumatic disease and discusses about different rheumatic arthritis that has been affected by MEFV gene mutations.

Material And Methods

Patients

During 16-years from 2003 to 2019 at pediatric rheumatologic clinic among 195 recorded files, 3 patients with diagnosis of RSH were reviewed thoroughly.

Patients had negative histories of FMF, JIA, gout, psoriasis, IBD, SLE, celiac and infectious causes such as brucellosis and some especial disorders such as Ehlers Danlos and joint hypermobility; post-infectious arthritis, pain amplification syndromes and osteochondrosis and palindromic rheumatism were excluded.

None of the patients and their first degree families had FMF and FMF related symptoms. Arthritis had been confirmed by imaging including MRI and or ultrasound further than laboratory tests. Tel-Hashomer criteria have been used to diagnosis of FMF. Patients had taken treatment in short course such as NSAID and Hydroxychloroquine (HCQ) intermittently as DMARDS with suspicion of unclassified and atypical JIA.

The study is complaint with the Helsinki Declaration and was approved by the local Ethics Committee under number (IR.ARUMS.-REC.1396.95). Written Informed consent was obtained from all the participants, and/or their parents.

MEFV gene mutation analysis

Peripheral blood was collected from patients and the samples were screened for the 12 common pathogenic variants (E148Q, P369S, F479 L, I692del, M680I (G/C), M680I (G/A), M694 V, M694I, K695R, V726A, A 744S, R 761H) by an RDB assay (FMF Strip Assay, Vienna lab, Vienna, Austria) according to manufacturer's instructions, from fresh blood sampling simultaneously at genetic lab center of the hospital.

Results

This study included three patients with relapsing arthritis that has been located on hip as a sole manifestation and diagnosed as recurrent synovitis of hip (RSH).

All data of patients and their findings and demographic characteristics are presented in Table 1.

Discussion

Articular involvement is one of the most common and significant features of FMF. Arthritis usually occurs during recurrences, which can be short-term and self-limiting in nature. It is usually presented as monoarthritis of the lower extremity in large joints. Sometimes arthritis is one of the first symptoms of FMF, and occasionally it is the only episodic symptom of disease in FMF patients. (5)

That is usually associated with fever, local redness, swelling and tenderness family history of FMF, positive mutations analysis, and favorable response to colchicine. (3). 5% of patients have recurrent protracted arthritis, usually of the hips or knees, with symptoms lasting a few months. (5)

Chronic destructive form usually involves weight-bearing joints such as the hips and knees. Chronic involvement of the hip is usually seen as repeated articular attacks or protracted attacks; however, chronic osteoarthritis of the hip joint can occur in patients without a history of attack at the affected joint (6)

Heller wrote the first comprehensive study about the arthritis in FMF patients, although his work confined to adult patients, he analyzed the clinical, roentgenologic, and histologic features of the articular manifestations of FMF. (7)

Eldar studied arthritis in 124 children with well-documented familial Mediterranean fever (FMF), 75% of the patients being under 10 years of age.

Arthritis was noted in the lower extremities 122 (98%), upper extremities 17 (14%), and small joints of the hands and feet 15 (12%). He report three patients with

atypical arthritis involving temporomandibular, sacroiliac, and sternoclavicular joints (3)

Recent findings have shown that the MEFV gene is associated with clinical conditions other than FMF. Screening of MEFV mutations in different rheumatic diseases evaluated the importance of this gene in those patients with arthritis other than FMF. (8).

Several case reports and cohorts suggest an association between FMF and certain inflammatory disorders, such as rheumatoid arthritis (9), JIA (10) systemic onset JIA (11), seronegative spondyloarthropathy (12.), Henoch-Schönlein purpura (13), polyarteritis nodosa (14), Behçet's disease (BD) (15), and Crohn disease (16).

It was shown that MEFV mutations in patients with RA were associated with more severe diseases (9). Furthermore, in Chinese and Indian patients with secondary amyloidosis, the prevalence of p.E148Q mutation was significantly higher than controls (17)

The allele frequencies of MEFV mutations were found to be 19.27%, in Turkish children with juvenile idiopathic arthritis which is higher than the general population. (10)

Enthesopathy and sacroiliitis occur in some FMF patients, and up to 7.5% of FMF patients are simultaneously diagnosed with AS. (18)

Gülhan's study showed that certain MEFV mutations may be acting as susceptibility factors for ERA. The presence of two patients with homozygous M694V mutations while they lacked other clinical features of FMF at diagnosis,

also suggests that ERA should be considered in FMF patients. (19)

It is a general consensus that spondyloarthropathy in FMF is negative for HLA-B27 and M694V might be a risk factor for AS. (12)

MEFV mutations are associated with “subclinical inflammation”; it has been showed by Tunca et al. (20) that, patients who were heterozygous for MEFV mutations have increased blood levels of inflammatory markers.

Like to Chetrit reports (21) which defined patients with MEFV-related non-FMF entities, these cases remind his new concept, and suggesting that the MEFV gene is associated with more than FMF.

This new concept regarding the MEFV gene and its link to such clinical phenotypes may lead to the existence of additional clinical presentations within the autoinflammatory diseases (22)

Furthermore, these MEFV gene mutation-associated syndromes will justify a therapeutic trial with colchicine as a main or adjacent drug. (21)

These patients diagnosed as RSH with relapsing and recurrent arthritis of hip showed MEFV gene mutations that include R761H, V726A, and A744S in heterozygote form which are not normal variants of healthy people. The most frequent variants among normal and healthy population of this area are E148Q (18.3%), followed by P369S (3.1%), V726A (2.2%), A744S (1.3%), (23)

Otherwise, our published data showed followings mutations as the most common variants alleles M694V (20.9%), V726A (12.7%), E148Q (10.7%), M680I (10.3%), M694I (2.1%), in FMF patients. (24)

Although transient synovitis of the hip is a common disorder in children, RSH is not a common condition. The presence of MEFV mutations in patients with RSH and its specific pattern, emphasis the potential role of this gene as a pathogenic background in this condition.

On the basis of possible role of MEFV gene in different rheumatic disease RSH could be considered as a MEFV gene related arthritis.

Although the outcome of children with one MEFV mutation and lack of FMF symptoms continues to be a challenge, periodic clinical visits, particularly if the child has a pathogenic MEFV mutation is recommended (25).

It is possible that these patients develop FMF related symptoms during their third and or more decades. If it occurs we will confront with a new dilemma; whether RSH is the first presentation of FMF related arthropathy, although it has not been reported up to now, and or it is a separate entity and co-existed with FMF. Because of the limited number of patients in this study a large sample size will be required to confirm this finding, however; RSH is not a common condition in children.

Conclusion

In our opinion, an idiopathic relapsing periodic arthritis in children with exclusively hip involvement (RSH) is a MEFV gene related arthropathy.

Abbreviations

FMF: Familial Mediterranean Fever; ERA: entesithis related arthritis; MEFV: Mediterranean fever Gene; PR: Palindromic Rheumatism; RSH: Recurrent Synovitis of Hip

Declarations

Declaration: There is not any declaration in this study.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals

Performed by any of the authors.

The study is complaint with the Helsinki Declaration and was approved by the local Ethics Committee under number (IR.ARUMS.REC.1396.95).

Informed consent was obtained from all parents individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

Please contact first author (Salehzadeh F.) for data request.

Competing interests

The authors declare that they have no competing interests.

Funding There is not any funding in this study.

Authors' contributions

FS: carried out the management and diagnosis of patients.

MM. Participated in the design of the study and performed the draft of manuscript. All authors read and approved the final manuscript.

Acknowledgements

None.

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Table

Data	Patient 1	Patient2	Patient3
Sex	female	male	female
Age at diagnosis	3.5 yr.	4 yr.	4.5 yr.
Duration of follow-up a (years)	4 yr.	5 yr.	7 yr.
Number of episodes per year	3-4	3	3-4
Attack intervals (mean) month	3 to 4 mo.	3 mo.	3to 4 mo.
Systemic symptoms during attacks	Low grade Fever	moderate Fever	Low grade Fever
Morning stiffness during attacks	No	No	No
MEFV Mutations	A744S	V726A	R761H
Average duration of episodes	3 days	3-4days	5 days
Joint /Right and left	Hip(R/L) intermittently	Hip(R/L) intermittently	Hip(R/L) intermittently

Table1.

Patient's findings and manifestations