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Letter to the Editor

Hip involvement in familial Mediterranean fever

Dear editor,

Familial Mediterranean fever (FMF) is a monogenic autoinflammatory disorder that is linked to homozygous mutations of the *MEFV* gene [1]. The field of FMF is expanding as many patients with FMF phenotype are heterozygous with monoallelic variants. Arthritis is a frequent manifestation of FMF, involving 50 to 75% of patients [2]. The hip is the third most commonly affected joint after the knee and ankle [2]. Aseptic necrosis of the femoral head [3] caused by disruption of local blood supply has also been reported in FMF patients. Meanwhile, hip inflammation or coxitis can be caused by axial spondyloarthritis, which develops at an increased rate in FMF patients [4,5]. Therefore, the literature is controversial as to whether coxitis in FMF is a distinct entity or a manifestation of an associated axial spondyloarthritis. Our objectives were to describe the clinical, functional and radiological features of hip involvement in FMF.

This observational study was based on data extracted from the JIR-cohort, an international multicenter data repository established by the National Commission on Informatics and Liberty (CNIL, authorization number N°: 914677). All patients included in this study were informed and gave written consent that data from their medical records might be used for research study in accordance with privacy rules. A systematic review was performed on PubMed and Embase on March 2020 without any language or period restriction using the generic keywords "coxitis" OR "hip" AND “familial Mediterranean fever".

35 articles from 1908 to 2017 presented original cases of FMF-associated coxitis and were included for analysis [6,7] (remaining references in supplementary data). Overall, 138 cases of coxitis were included, including 7 cases from 5 French new patients. Ninety-four patients were reported for a total of 119 hips, while hips rather than patients were reported for the remaining 19 cases. Lateralization was known for 56 patients, of which 20 (36%) suffered from bilateral hip involvement. Mean age at presentation was 28.7 years (n=54, median 27 years). Mean age at onset of symptoms was 19.2 years (n=42, median 18.5 years). *MEFV* genotype was available for 11 patients, revealing M694V homozygosity (n=10) and M694V/I692del compound heterozygosity (n=1).

Overall, chronic impairment developed in 73% (69/94) of patients and 75% (103/138) of hips.

We identified 4 different natural histories for hip involvement. Protractile arthritis (Fig. 1A, n=39 patients, 41%; n=66 hips, 48%) is an acute attack lasting more than 3 weeks with major functional impairment, forcing the patient to stay bedridden. Chronic disability developed in 90% of patients and 89% (n=59) of hips. The second and third patterns both consist of remittent attacks with symptom-free intervals. The second pattern leads to chronic impairment (Fig. 1B, n=22 patients, 23%; n=29 hips, 21%), while the third one does not (Fig. 1C, n=21 patients, 22%; n=28 hips, 20%). The fourth subgroup of patients experienced progressive mechanical pain without acute exacerbations (Fig. 1D, n=12 patients, 13%; n=15 hips, 11%), despite presence of radiological signs of inflammation.

Associated conditions consisted of ankylosing spondylitis confirmed by the modified New York criteria or axial spondyloarthritis according to the ASAS criteria [8] (n=11 patients, 12%; n=16 hips, 12%), isolated sacroiliitis (n=2 patients, 2%; n=3 hips, 2%), and juvenile idiopathic arthritis (n=1 patient, 1%; n=2 hips, 1.5%). Axial spondyloarthritis or isolated sacroiliitis associated with FMF and coxitis (Fig. 1G) were remarkable by their absence of spinal involvement (12/13 patients) and negative HLA-B27 status (0/13 patients). Extra-axial signs, namely knee or ankle arthritis or enthesitis, were frequent (9/13). BASDAI was rarely reported (n=2). When coxitis was associated with sacroiliitis, mean age at onset of symptoms was higher (30.5 vs 19.2 years), chronicity was more prevalent (92% vs 68% of patients), and protractile arthritis was less frequent (23% vs 39% of patients).

Radiographic and CT imaging showed joint space narrowing (n=24 hips), demineralization (n=10), and femoral head osteonecrosis (n=10). Hip MRI (n=11) showed bone edema (n=6, Fig. 1E), surrounding tissues and muscles edema (n=3), joint effusion (n=5, Fig. 1F), synovial enhancement with gadolinium (n=1), and femoral head osteonecrosis (n=4).

Most patients were not taking (78%, n=36) or had recently stopped taking (n=1, 2%) colchicine when hip inflammation developed. Upon diagnosis of coxitis, introduction of colchicine for previous non-users (86%, n=6/7) or an increase in its posology (n=1/1) was almost always efficient for pain relief and functional improvement. Non-steroidal anti-inflammatory drugs yielded results (5 failures, 2 successes), and disease-modifying anti-rheumatic drugs were always inefficient (hydroxychloroquine n=1; methotrexate n=2). Although intraarticular corticosteroid injection provided relief in 2 cases, they did not prevent recurrence of symptoms. Canakinumab decreased pain and improved hip mobility in one case who had developed chronic impairment. Infliximab therapy was attempted in 2 patients, being efficient in one of them. Development of secondary osteoarthritis may have accounted for treatment failure in the second case.

Twenty-five patients (27%) underwent at least one hip arthroplasty, while 51 hips (37%) were treated with a total of 56 arthroplasties. Mean age at first arthroplasty was 28.4 years (n=11). The mean delay between onset of symptoms and first arthroplasty was 7 years (n=11, median 6 years).

Our study shows that FMF-associated hip disease is remarkable for its risk of chronicity, in contrast to other joints involved in FMF. Protractile arthritis has a particularly poor prognosis with a 90% risk of chronic impairment. In contrast, 87% of patients with protractile arthritis of the knee underwent full functional recovery in Sneh *et al*'s series [6]. Classical acute but resolutive attacks of arthritis also bear a considerable

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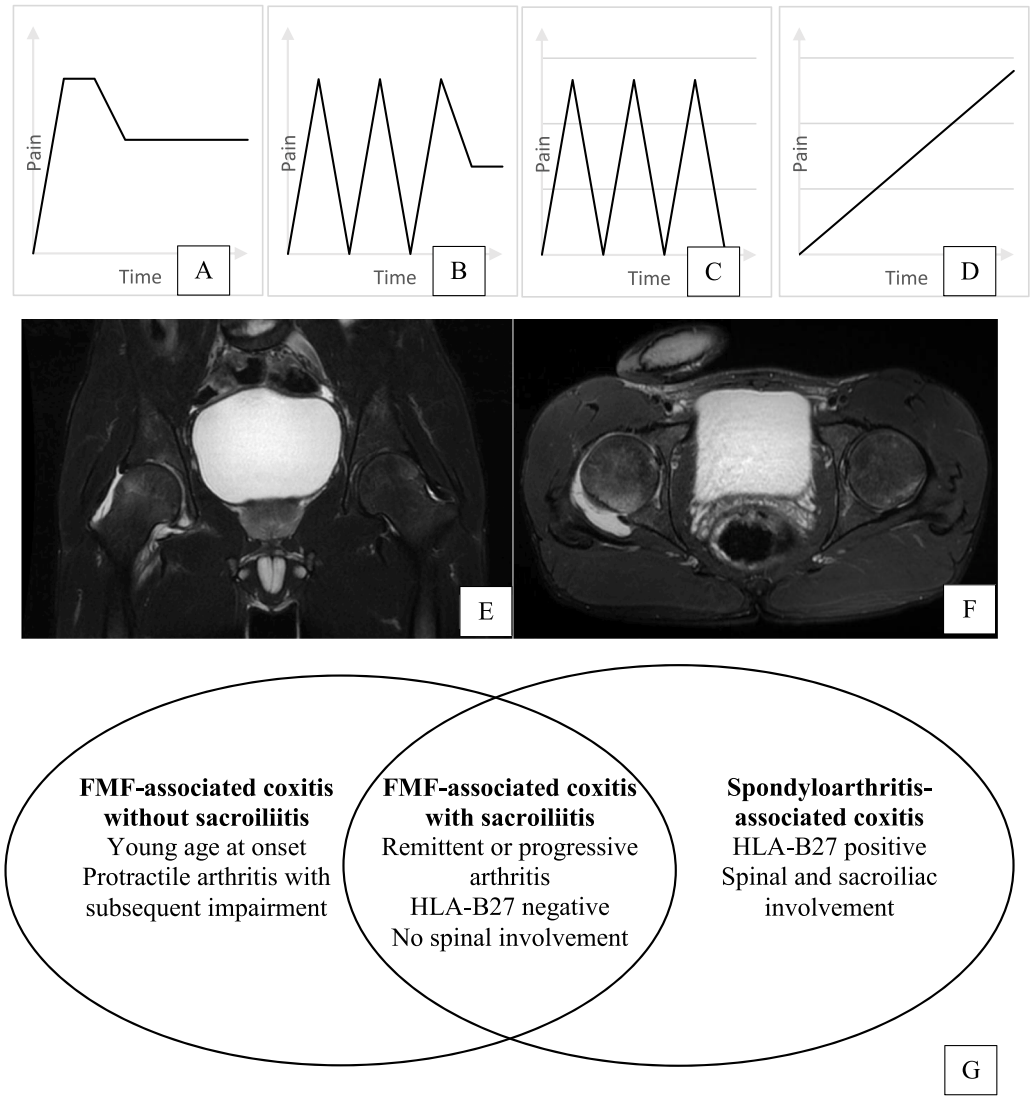

Fig. 1. A–D. Natural histories of FMF-associated coxitis. A: protractile arthritis. B: remittent arthritis with chronic impairment. C: remittent arthritis without chronic impairment. D: insidious progressive arthritis. E, F: Hip MRI of patient 5 during an attack. Right femoral edema and intraarticular hip effusion are visible as hypersignals on T2 STIR sequences. G: Venn diagram showing the overlap between FMF-associated coxitis and spondyloarthritis

risk of chronicity of approximately 50%. Finally, progressive and insidious impairment without acute episodes of arthritis is a possible presentation of hip involvement in FMF. In the latter situation, the discordance between the mechanical pain pattern and the presence of inflammatory lesions on imaging can be confusing and lead to diagnostic delay. Analysis of the 11 available genotypes revealed that all patients bore at least one copy of the M694V allele. Thus, presence of the M694V allele should allow the clinician to define a subgroup of FMF patients at high risk for coxitis warranting active screening.

In our review, prevalence of sacroiliitis (14%) and axial spondyloarthritis (12%) in FMF-associated coxitis was higher than the prevalence reported in studies pertaining to the general FMF population (7% for sacroillitis in a Turkish cohort of 256 patients [4]). Our review showed that FMF patients with both coxitis and sacroiliitis had later onset of symptoms (30.5 versus 19.2 years old), less frequently suffered from protractile arthritis (23% versus 39%) and were more likely to develop chronic impairment (92% versus 68%) than FMF patients without sacroiliitis. These elements suggest that within the FMF-spondyloarthritis overlap group, the natural course of coxitis resembles the one of the general spondyloarthritis population. Nevertheless, spondyloarthritis in FMF bears atypical features, namely a negative HLA-B27 status and a lower prevalence of vertebral involvement compared to spondyloarthritis in the general population [4,5] (Fig. 1G). While 37% of FMF-associated coxitis required arthroplasty, a recent retrospective study estimated the rate of arthroplasty in spondyloarthritis-associated coxitis between 5 and 8% [9]. This discrepancy is in favor of the idiosyncratic nature of coxitis in FMF when occurring in the absence of spondyloarthritis.

In conclusion, clinicians should systematically and specifically inquire about symptoms and signs of hip inflammation in FMF patients. If those are present, imaging should be performed. Once diagnosed, coxitis should be closely monitored and actively treated.

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.11.008.

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