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A corner for a hot dilemma in familial Mediterranean fever

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The dilemma

i. Should we treat asymptomatic carriers of 2 mutations in the *MEFV* gene?
ii. Should we screen asymptomatic siblings of a carrier of 2 *MEFV* mutations?

Case presentation

A 32-year-old gynaecologist came to my clinic (E. Ben-Chetrit) at 26 weeks of her pregnancy. She already has two healthy daughters, ages 4 and 2.
She had decided on her own to have an exome analysis of her foetus. Her future baby was found to be a carrier of two *MEFV* mutations: A744S and V726A.
Looking at this result both parents had a genetic test for *MEFV* mutations too. The mother was found to carry a single variant A744S while her husband carried the V726A mutation. Both were asymptomatic. The husband was an Ashkenazi Jew whereas the mother was of combined origin of Ashkenazi and Moroccan.
The parents asked me (E. Ben-Chetrit) two questions:
1. Does the foetus have familial Mediterranean fever (FMF) based on carrying 2 mutations and should they start treating him with colchicine immediately after delivery?
2. Should they screen their 2 daughters for *MEFV* mutations?

Discussion

Genetically, since the foetus carries 2 mutations, the baby may develop FMF clinically. Though mutation A744S is considered a genetic variant of uncertain significance (VOUS), the combination with a pathogenic mutation (V726A) increases the risk of having symptomatic FMF.
The question is whether we should start colchicine in the baby once he is born or whether we should wait and treat him only if he becomes symptomatic.
Usually, we treat FMF patients following their diagnosis and when they are already symptomatic. Therefore, the question is why should we treat an asymptomatic individual who carries 2 mutations?
One reason for that has been the observation that there are patients who present with proteinuria (due to renal amyloidosis) without expressing any previous typical symptoms of FMF (type II FMF).
The first description of such patients was that by Blum *et al*. who proposed that there were patients with amyloidosis as the sole manifestation of FMF (1). Later, Sohar *et al*. describe 8 patients with type II FMF, 3 of whom developed symptoms of FMF later (2). The duration of follow-up in this study was only 3 years. In a retrospective study, Saatci *et al*. reported that out of 180 children with amyloidosis there were 123 who had FMF. The authors considered the remaining 57 as having type II FMF. On the other hand, it is not clear what convinced the authors that the 57 patients in the second group had type II FMF rather than amyloidosis associated with other conditions. In fact, the same article lists associated diseases with either type I or type II FMF patients which include 9 patients with juvenile rheumatoid arthritis (JRA), a condition well known to cause amyloidosis. In another retrospective study, Balci *et al*. looked for the *MEFV* gene mutations in FMF phenotype II children with renal amyloidosis (4). They found that in phenotype II amyloidosis patients, the distribution of the four common *MEFV* mutations (M694V, M680I, V726A, and E148Q) was not significantly different from that found in all FMF patients with typical symptoms who do not develop amyloidosis. Therefore, they suggest that secondary genetic or environmental factors are operative in the development of secondary amyloidosis in patients with FMF. However, some studies raised doubt as to the existence of phenotype II FMF. Majeed *et al*. observed no case of phenotype II in their series of 476 patients (5). Melikoglu *et al*. also conducted a survey of phenotype II in FMF among the 461 relatives of 13 patients with FMF and amyloidosis and 269 relatives of 8 juvenile chronic arthritis (JCA) patients with amyloidosis (6). No individual with type II amyloidosis could be identified.
It should be emphasised that none of the above studies mentioned the rate of subclinical acute phase reactants (CRP, ESR or SAA) in these patients. We need to know about these acute phase reac-

tants since the assumption is that amyloidosis develops in FMF patients due to continuous inflammation when severe enough, causes recurrent attacks. In the case of type II FMF, the assumption is that the patients do have a continuous subclinical inflammatory process that does not evolve into a full-blown FMF attack but is enough to cause deposition of serum amyloid A (SAA) leading to amyloidosis. This can surely be investigated by measuring the CRP, ESR, and SAA levels in the blood.

Thus, we can perhaps redefine the patients with type II FMF as those individuals who present with proteinuria due to renal amyloidosis without any history of typical symptoms of FMF, but with evidence of an underlying sub-clinical inflammatory process documented by elevated acute phase reactants.

The development of amyloidosis is dependent mainly on the type of *MEFV* mutations the patient carries. Nevertheless, there are a few more contributive factors for the development of this complication. Among others, we should mention: the presence of a close family history of amyloidosis, carriage of specific SAA gene polymorphisms, male gender, and the country of origin of the patient.

In an effort to give a more comprehensive answer to the questions posed, we have conducted a small questionnaire e-poll among 13 Israeli and 13 Turkish physicians in FMF. We asked them to give us their response to the parents' query:

1. ***Should we treat asymptomatic carriers of 2 mutations in the MEFV gene?***

2. ***Should we screen asymptomatic siblings of a carrier of 2 MEFV mutations?***

The possible answers for Question 1 were:

a. Treat
b. Do not treat
c. It depends upon the combination of mutations

The possible answers for Question 2 were:

a. Yes
b. No

A space for free text for those who want to add any comments or remarks was also allowed.

The results of the poll were as follows: of the 13 Israeli physicians, 12 responded, all of whom claimed that they would not treat an asymptomatic patient, no matter which mutations he carries. Regarding the genetic screening of the daughters, 10 physicians would not screen the 2 daughters for *MEFV* mutations while 2 physicians would do it.

Of the 13 Turkish physicians only 10 responded. Of these, 5 physicians would treat the patient depending upon the combination of mutations (*e.g.* homozygous for M694V mutation) whereas 5 would not. Regarding screening the asymptomatic siblings, 6 would not perform genetic testing whereas 4 would recommend screening. These results show that the answers to the questions are not that clear or obvious.

Our proposed answers

Based upon our current knowledge and the available data, here is our proposal for answering the parents.

Since there are no data regarding the size of the risk for amyloidosis in asymptomatic carriers of 2 mutations, who do not have a subclinical elevation of acute phase reactant (CRP, ESR SAA), there is no justification to start colchicine no matter which combination the patient carries. This approach may change if this individual carries two pathogenic mutations such as (M694V or M680I) and has a close family history of amyloidosis. In this case, colchicine treatment may be considered immediately after birth.

In all asymptomatic new-borns carrying 2 mutations, we should monitor them for clinical symptoms and inflammatory parameters in the blood with urinalysis every 3–6 months. Once they have either clinical symptoms or elevated acute phase reactant, we should start colchicine treatment.

Regarding screening asymptomatic siblings, we usually do not recommend screening them for *MEFV* mutations or variants. Apart from pure medical reasons, this is because of moral, judicial and ethical problems in addition to causing the family stressful situations following the results of positive carriers. However, if we find that they have elevated CRP, ESR, or SAA in 2 consecutive blood tests in intervals of 2-3 months without any other explanation (an underlying infection or non-FMF inflammation), then we have both the medical and the moral justification to do genetic tests even in these asymptomatic siblings

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