ABSTRACT

Objectives. Familial Mediterranean fever (FMF) causes recurrent episodes of fever and painful serositis. It has been suggested that FMF can cause recurrent aseptic meningitis (RAM). Due to the rarity of both diseases, this claim cannot be assessed with epidemiological methods. We therefore decided to perform a systematic review of the literature to assess the number and validity of published case reports.

Methods. Medline, Embase, Pascal, Web of Science and the proceedings of relevant conferences were searched. Two independent investigators selected reports asserting RAM in FMF patients, abstracted data and rated the strength of evidence with a custom tool designed to assess: (a) the diagnosis of FMF; (b) the diagnosis of RAM; and (c) the link between FMF and RAM. A causal link was supported by (i) evidence of inflammation and/or clinical FMF features during episodes of RAM; (ii) effectiveness of colchicine to prevent further bouts of meningitis; and (iii) the exclusion of other causes of RAM.

Results. Among 944 retrieved references, 917 were rejected by title and abstract screening and 15 after full text review. The strength of evidence of 12 alleged cases of RAM due to FMF was assessed. FMF was unsupported in 4 cases and RAM in 3 further cases. Four of the 5 remaining cases did not provide adequate evidence to support a causal relationship between FMF and RAM.

Conclusion. The possibility of RAM due to FMF is poorly supported by a single fairly documented case report that does not, however, meet current diagnostic standards.
sides over a mean observation time of 12 years (16). However, the 95% confidence interval of this observed prevalence ranges from 0 to 31/100,000; the true prevalence of RAM in FMF patients could therefore be less, equal or up to 10 times higher than the 2.2/100,000 observed in an unselected population (7). To reach a definite conclusion, an epidemiological study would have to include several 10,000 of FMF patients observed over a long period of time. Such a study is unlikely to be performed in the near future.

Case reports are therefore the best available evidence to support FMF as a cause of RAM in children and adults. Our aim was to outline the features of what would be a convincing case report of RAM caused by FMF and to perform a systematic review of the literature to assess all published case reports against this gold standard.

Materials and methods
A systematic review of cases reported in the literature was conducted to retrieve all cases of RAM linked to FMF and assess their validity. These cases could be embedded in any type of clinical study but it turned out that only case reports had been published on this topic. Medline, Embase, Pascal and Web of Science were searched without language restrictions or time limit up to February 2012. Search terms were “Familial Mediterranean Fever” and synonyms (like “Mediterranean familial fever”, “periodic disease” or “periodic fever” and “Meningitis” or “cerebrospinal fluid”). For instance, Medline was searched using the following query: (“Familial Mediterranean Fever”[tw] OR “Mediterranean familial fever”[tiab] OR “periodic disease”[tiab] OR “periodic fever”[tiab]) AND (“Meningitis”[tw] OR “cerebrospinal fluid”[tw]). The research was extended to the proceedings of relevant conferences and the refer-

Table I. Simplified criteria for the diagnosis of familial Mediterranean fever (adapted from Livneh et al. [17]).

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Typical attacks</td>
<td>1. Atypical attacks involving one or more of the following sites</td>
</tr>
<tr>
<td>a. peritonitis (generalised)</td>
<td>a. chest</td>
</tr>
<tr>
<td>b. pleuritis (unilateral) or pericarditis</td>
<td>b. joints</td>
</tr>
<tr>
<td>c. monoarthritis (hip, knee, ankle)</td>
<td>2. Exertional leg pain</td>
</tr>
<tr>
<td>d. fever alone</td>
<td>3. Favourable response to colchicine</td>
</tr>
<tr>
<td>2. Atypical abdominal attack</td>
<td></td>
</tr>
</tbody>
</table>

Typical and atypical attacks (attacks that are neither typical nor atypical are not taken into account)

- Typical attacks must fulfill the following criteria:
  1. Recurrence (at least three attacks of the same type)
  2. Fever (rectal temperature of 100°F or more)
  3. Limited duration (between 12 hours and 3 days)

- Atypical attacks are recurrent and painful but with at least one of the following features:
  1. Rectal temperature below 100°F
  2. Attacks are shorter than 12 hours or longer than 3 days, but last more than 6 hours and less than a week
  3. Absence of clinical sign of peritonitis during abdominal attacks
  4. Localised abdominal attacks
  5. Attacks involving other joints than the specified ones

Records identified by database searching (n = 931)
Records screened (n = 944)
Records excluded (n = 917)
- Meningitis but no FMF (592)
- FMF but no meningitis (3)
- No FMF and no meningitis (264)
- Review articles (53)
- Other (5): 1 basic research, 2 opinion pieces, 1 veterinary medicine and 1 history of medicine.

Full-text articles assessed for eligibility (n = 27)

Fig. 1. Flow diagram depicting the selection process.

Studies included in the qualitative synthesis (n = 12)
- No FMF (3)
- No RAM (7)
- Neither FMF nor RAM (3)
- Review (2)

Additional records identified in other sources (n = 13)
First, two independent investigators screened titles and abstracts of retrieved references to exclude those that clearly were unrelated to FMF, unrelated to meningitis or that did not report original cases. Remaining articles were then retrieved for full-text review by the same two investigators. Articles were selected only if they claimed to report original cases of recurrent meningitis in FMF patients.

Relevant data were abstracted from the selected articles, their completeness was evaluated and the diagnoses of FMF and RAM were critically assessed. We evaluated the completeness of documentation regarding five critical features: (a) patients’ ethnicity; (b) daily dose of colchicine; (c) frequency

**Table II.** Completeness of the documentation (1: information reported; 0: information not reported).

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Daily dose of colchicine</th>
<th>Number of FMF attacks higher than 2*</th>
<th>Acute phase reactant level during FMF attacks</th>
<th>Acute phase reactant during meningitis</th>
<th>Completeness of documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barakat et al. 1988 (34)</td>
<td>1</td>
<td>(1)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Collard et al. 1991 (43)</td>
<td>1</td>
<td>(1)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gedalia et al. 1993 (40)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>George et al. 1965 (35)</td>
<td>1</td>
<td>not relevant</td>
<td>(1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Goksel et al. 1962 (36)</td>
<td>0</td>
<td>not relevant</td>
<td>(1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Karachalious et al. 2005 (33)</td>
<td>1</td>
<td>1</td>
<td>(1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ota et al. 1986 (19)</td>
<td>0</td>
<td>1</td>
<td>(1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ocklitz et al. 1972 (37)</td>
<td>0</td>
<td>not relevant</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ramadan et al. 1994 (39)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schwabe et al. 1988 (41)</td>
<td>1</td>
<td>0</td>
<td>(1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Somers et al. 1957 (38)</td>
<td>0</td>
<td>not relevant</td>
<td>(1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vilaseca et al. 1982 (42)</td>
<td>0</td>
<td>1</td>
<td>(1)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* (1) if the information is not explicitly stated but there are good reasons to believe that more than 2 attacks occurred.

**Table III.** Application of diagnostic criteria of FMF and RAM to selected case reports (1: criterion satisfied; 0: criterion unsatisfied; ?: criterion not reported).

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Major criteria for FMF diagnosis</th>
<th>Minor criteria for FMF diagnosis</th>
<th>Diagnosis of FMF</th>
<th>At least 3 episodes of self limiting meningitis</th>
<th>Inflammatory CSF on at least two distinct occasions</th>
<th>Negative CSF bacterial (and fungal) cultures</th>
<th>Diagnosis of RAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barakat et al. 1988 (34)</td>
<td>Syrian</td>
<td>Typical abdominal</td>
<td>Atypical chest</td>
<td>Response to colchicine (1mg/d)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Collard et al. 1991 (43)</td>
<td>Moroccan</td>
<td>Typical arthritis Atypical</td>
<td>Atypical chest</td>
<td>Response to colchicine (1.2 mg/d)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gedalia et al. 1993 (40)</td>
<td>?</td>
<td>Abdominal</td>
<td>Atypical</td>
<td>Arthritis Response to colchicine (dose unknown)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>George et al. 1965 (35)</td>
<td>?</td>
<td>0</td>
<td>Atypical</td>
<td>Heart Response to colchicine (dose unknown)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Goksel et al. 1962 (36)</td>
<td>?</td>
<td>0</td>
<td>Atypical</td>
<td>Arthritis Response to colchicine (dose unknown)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Karachalious et al. 2005 (33)</td>
<td>Caucasian</td>
<td>Abdominal</td>
<td>Atypical</td>
<td>Arthritis Response to colchicine (1.8 mg/d)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ota et al. 1986 (19)</td>
<td>Japanese</td>
<td>Typical fever</td>
<td>Response to colchicine (1 mg/d)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Ocklitz et al. 1972 (37)</td>
<td>?</td>
<td>0</td>
<td>Atypical</td>
<td>Heart Response to colchicine (dose unknown)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ramadan et al. 1994 (39)</td>
<td>Mediterranean</td>
<td>Typical arthritis Atypical</td>
<td>Atypical</td>
<td>Arthritis Response to colchicine (dose unknown)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Schwabe et al. 1988 (41)</td>
<td>Moroccan</td>
<td>Abdominal</td>
<td>Atypical</td>
<td>Arthritis Response to colchicine (dose unknown)</td>
<td>1</td>
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<td>1</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>Vilaseca et al. 1982 (42)</td>
<td>?</td>
<td>Typical arthritis</td>
<td>Response to colchicine (1 mg/d)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
of FMF attacks; (d) level of acute phase reactants during FMF attacks without meningitis; (e) level of acute phase reactants during meningitis.

Diagnosis of FMF was ascertained using validated clinical criteria, which have a sensitivity of 99% and a specificity of 98% in patients of Mediterranean origin (17) (Table I). Three components were requested for the diagnosis of RAM: (a) at least 3 episodes of meningitis without other persistent neurologic abnormalities, separated by asymptomatic intervals and resolving spontaneously without sequelae; (b) increased CSF white blood cell count found in at least two distinct clinical episodes of meningitis; (c) negative CSF bacterial cultures (6, 18).

The link between FMF and RAM was evaluated with a custom tool when both diseases were convincingly diagnosed. A causal link was supported by: (a) marked elevation of acute phase reactants and/or painful serositis (peritonitis, pleuritis, pepticulitis or arthritis) during episodes of RAM; (b) effectiveness of colchicine to prevent further bouts of meningitis; (c) exclusion of other causes of RAM. Other causes we expected to see excluded were at least: (c.i) drug hypersensitivity (medical history); (c.ii) HSV-2 (PCR or serology in the CSF); (c.iii) other systemic diseases including Behçet’s disease, Vogt-Koyanagi-Harada’s disease, lupus erythematosus and Sjögren’s syndrome (medical history and physical examination); (c.iii) cystic lesions (brain imaging).

**Results**

The selection process is depicted in the flow diagram (Fig. 1). Among 944 retrieved references, 917 were rejected after title and abstract screening. The full-text of twenty-six articles and one conference’s proceedings were retrieved, including one Japanese article rated on its English abstract only (19). Fifteen were rejected because they were either not about FMF, nor about RAM, or both (13, 14, 20-32).

The 12 remaining articles claimed to report cases of RAM in FMF patients (see web only supplementary file for short case summaries). Completeness of documentation was evaluated in these articles (Table II) and the strength of evidence was assessed (Tables III and IV). Important data was missing in 9 cases and complete in only 3 cases (33-35). Provided data did not properly support FMF in 4 cases (35-38) and RAM in 3 further cases (19,39,40) (Table II). One of the 5 remaining cases did not report elevated acute phase reactants and/or clinical FMF features during episodes of RAM (33). Colchicine prevented RAM in 3 of the 4 other cases (34,41,42) but was inefficient in 1 (43). Only 1 case ruled out the other causes of RAM, as requested by the predefined criteria (34).

**Discussion**

We outlined the features of what could be regarded as a convincing case report of RAM caused by FMF, regarding completeness of documentation, appropriateness of diagnostic criteria and supporting evidence for a causal relationship. We undertook a systematic review of the literature and found 12 articles claiming to report RAM due to FMF, but most cases were improperly reported and were compatible with other diagnostic hypotheses.

**Table IV. Strength of the evidence supporting causality in convincing cases of FMF associated with RAM (1: criterion satisfied; 0: criterion unsatisfied; ?: criterion not reported).**

| Barakat et al. 1988 (34) | 1 (inflammation and clinical) | 1 | 1 | 1 (serology) | 1 (CT scan) | 1 | 1 |
| Collard et al. 1991 (43) | 1 (inflammation) | 0 | 1 | 0 | 0 | 1 | 0 |
| Karachaliou et al. 2005 (33) | 0 | 1 | 1 | 1 (serology) | 1 (CT scan) | 1 | 0 |
| Schwabe et al. 1988 (41) | 1 (inflammation) | 1 | 1 | 0 | 1 (CT scan) | 1 | 0 |

FMF or RAM were doubtful in 7/12 case reports. These 5 remaining case reports show that the two diseases can concur, but a causal relationship remains uncertain at this point. Statistical analysis can be used to support causation at the group level but is obviously unhelpful to assess single cases. We considered three lines of evidence supporting a causal relationship at the individual level: (a) episodes of RAM due to FMF should be accompanied by other clinical or biological features of FMF attacks; (b) colchicine, which efficacy is well established to prevent or lessen acute attacks of FMF, should prevent or lessen episodes of RAM due to FMF; and (c) other classical causes of RAM (drugs, HSV2 infection, systemic diseases and cystic brain lesions) should be ruled out. Methodological assessment showed that only 4 cases satisfied the first criterion, 3 met the first and the second criteria and only 1 met all the three of them (34) and truly supports causation (Table III).

The evidence supporting FMF, RAM and causation in the case reports has been evaluated with respect to the diagnostic standards prevailing when the cases were reported. However, these standards would be regarded as inadequate nowadays. The diagnostic criteria of FMF proposed by Livneh et al. have high sensitivity and specificity in Mediterranean populations (17), but the ethnic background of patients was not always reported. Although three attacks must occur at the same location to fulfill the criteria (17), their exact number was never reported and the diagnosis was accepted if attacks were reported as frequent or recurrent. Moreover, genetic testing is now required to support.
the diagnosis of FMF (4, 5). PCR in the CSF is now required to rule out HSV2 meningitis (6, 18). Although the diagnoses of Behget’s and Vogt-Koyanagi-Harada’s diseases are mostly clinical, fundoscopy should be performed to rule out posterior uveitis or retinal vasculitis (44, 45). Besides clinical examination, laboratory tests (antinuclear antibodies, serum complement levels) are often requested to rule out lupus erythematosus and Sjögren’s disease (46, 47). Furthermore, brain MRI has higher sensitivity than brain CT scan to diagnose cystic brain lesions (48).

Unfortunately, even the most convincing case did not ascertain FMF with genetic testing, did not rule out HSV2 meningitis with PCR, did not rule out system disease with ophtalmological examination and laboratory tests, and did not exclude structural brain abnormalities with MRI (34). Moreover, the first episode of aseptic meningitis occurred after metaraminol administration, which could raise the hypothesis of drug induced meningitis. However, metaraminol is not known to be a cause of aseptic meningitis and is regarded by some authors as a trigger of FMF attacks that can be used for diagnostic purposes (49). The first episode of meningitis (after metaraminol injection) was associated with an abdominal attack, unlike typical drug-induced meningitis; further episodes of meningitis, also associated with abdominal attacks, occurred without new exposure to metaraminol.

Whether the association between FMF and RAM is causal or fortuitous has already been discussed in case reports and reviews (16, 41-43, 50). Unfortunately, the lack of epidemiological data and the lack of appropriate critical appraisal of the whole available anecdotal evidence has hampered a proper answer to this question. We considered that well documented single cases can support causality if they meet appropriate criteria that we tried to capture for our study question (51-54). Consistently with our structured assessment, several experts have considered the case reported by Barakat et al. (34) as one of the most convincing ones (16, 50). Our review has several limitations.

Firstly, critical appraisal was limited, as always, by the completeness of the documentation. In other words, we could only assess what the authors wrote and not what actually was the case. Authors may have omitted either positive or negative signs and it may be that several cases judged as unconvincing would not have been if adequately reported. Secondly, diagnostic criteria are always open to discussion. For instance, Livneh et al. criteria have not been validated in patients of non-Mediterranean origin (17). Colchicine responsiveness is another problematic item, depending among others on prescribed daily doses and on patient’s compliance. Nonetheless, diagnostic criteria are unavoidable for standardized research purposes. Thirdly, we excluded sporadic aseptic meningitis from our review, because recurrence is a main feature of acute FMF manifestations (17).

Conclusion
To conclude, there is no available evidence to properly support RAM as a manifestation of FMF. Due to the rarity of both FMF and RAM, epidemiological evidence for or against a causal relationship is unlikely to be available in the near future. A systematic review of the literature located a few reports of patients with both FMF and RAM, but the evidence provided to support a causal association was insufficient in all cases.

Authors wishing to publish a convincing case report of RAM caused by FMF should adhere to the features outlined in this review, regarding completeness of documentation, appropriateness of diagnostic criteria and supporting evidence for a causal relationship. In particular, they should ascertain FMF by genetic testing and conscientiously rule out other causes of RAM in patients with FMF, including HSV 2 (by PCR in the cerebrospinal fluid), drug-induced meningitis (by a careful review of prescription and non-prescription drugs), and cystic brain lesions (with MRI). Until such a case is reported, clinicians diagnosing RAM in FMF patients should consider that another cause must be sought.

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