Is recurrent aseptic meningitis a manifestation of familial Mediterranean fever? A systematic review

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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.*

Introduction

Familial Mediterranean fever (FMF) is of autosomal dominant inheritance and associated with mutations of the MEditerranean FeVer (*MEFV*) gene. It usually manifests in childhood (before the age of 20) and causes recurrent acute attacks of fever with serositis (peritonitis, pleuritis, pericarditis or synovitis) and erysipelas-like skin lesions (1, 2). The attacks are associated with elevated acute phase reactants and are prevented by daily colchicine intake (3). Genetic testing is now available (4, 5), but the diagnosis of FMF has long been clinical, based on various sets of criteria.

Recurrent aseptic meningitis (RAM) is defined by recurrent episodes of fever and meningitis lasting 2 to 5 days with spontaneous recovery (6). The number of episodes usually ranges from 3 to 10 and HSV-2 infection is regarded as the most common cause (6). A prevalence of 2.2/100,000 has been reported in an adult population observed over a period of 10 years (7). Other causes have been reported, most notably prescription and non prescription drugs (8) and dermoid cysts (9). Systemic diseases, like Behçet's disease, Vogt-Koyanagi-Harada's disease, systemic lupus erythematosus and Sjögren syndrome, occasionally present as recurrent aseptic meningitis (10-12).

Before being recognised as a manifestation of HSV-2 infection, RAM has been classified as a "periodic disease" (13, 14). This nosological category was not well understood, but FMF was regarded as its prototype (15). Moreover, meninges and serous membranes have the same embryological origin (mesoderm). For both reasons it has been suggested that FMF can cause recurrent meningitis, but this claim is disputed among experts.

Seven patients from a database of 12,000 adults with FMF experienced a single episode of aseptic meningitis, but none of them had recurrent epi-

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

Major and minor criteria	
Major criteria	*Minor criteria*
1. Typical attacks	1. Atypical attacks involving one or more of the following sites
a. peritonitis (generalised)	a. chest
b. pleuritis (unilateral) or pericarditis	b. joints
c. monoarthritis (hip, knee, ankle)	2. Exertional leg pain
d. fever alone	3. Favourable response to colchicine
2. Atypical abdominal attack	
Typical and atypical attacks (attacks that are neither typical nor atypical are not taken into account)	
Typical attacks must fulfill the following criteria:	*Atypical attacks are recurrent and painful but with at least one of the following features:*
1. Recurrence (at least three attacks of the same type)	1. Rectal temperature below 100°F
2. Fever (rectal temperature of 100°F or more)	2. Attacks are shorter than 12 hours or longer than 3 days, but last more than 6 hours and less than a week
3. Limited duration (between 12 hours and 3 days)	3. Absence of clinical sign of peritonitis during abdominal attacks
	4. Localised abdominal attacks
	5. Attacks involving other joints than the specified ones

sodes 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-

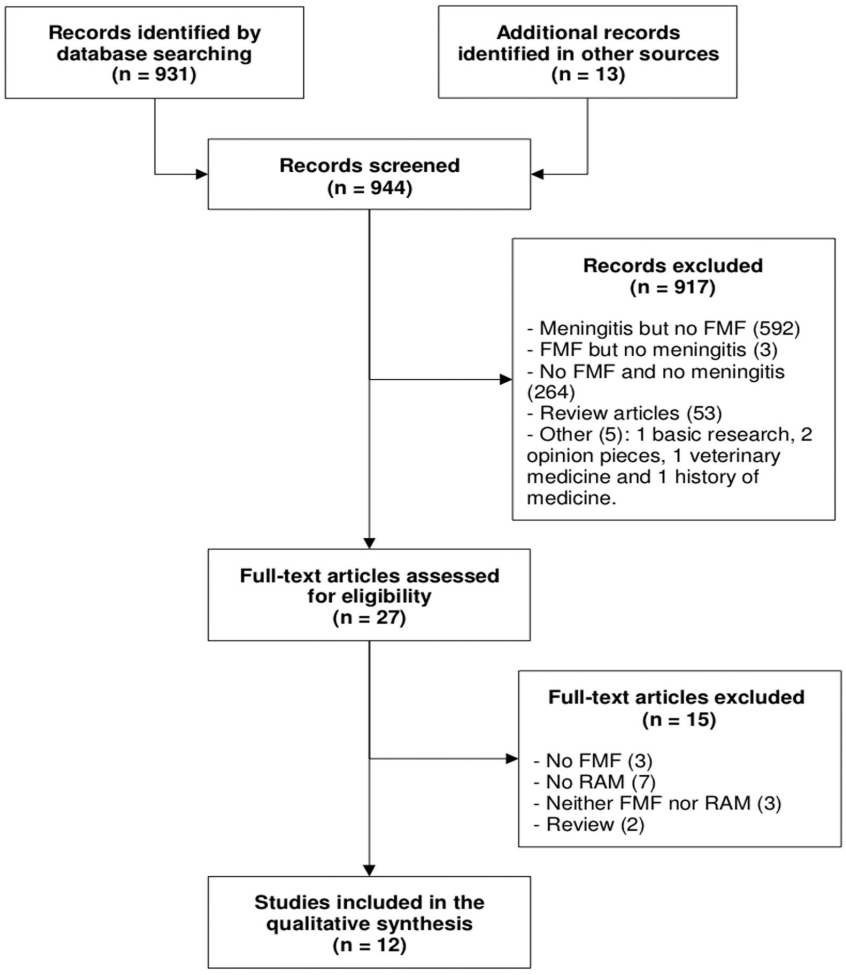

Fig. 1. Flow diagram depicting the selection process.

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

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

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

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

	Ethnicity	Major criteria for FMF diagnosis	Minor criteria for FMF diagnosis	Diagnosis of FMF	At least 3 episodes of self remitting meningitis	Inflammatory CSF on at least two distinct occasions	Negative CSF bacterial (and fungal) cultures	Diagnosis of RAM
Barakat *et al*. 1988 (34)	Syrian	Typical abdominal	Atypical chest Response to colchicine (1mg/d)	**1**	1	1	1	**1**
Collard *et al*. 1991 (43)	Moroccan	Typical arthritis Atypical abdominal	Atypical chest Response to colchicine (1.2 mg/d)	**1**	1	1	1	**1**
Gedalia *et al*. 1993 (40)	?	Atypical abdominal	Atypical arthritis Response to colchicine (dose unkwown)	**1**	0	1	1	**1**
George *et al*. 1965 (35)	?	0	Atypical chest	**0**	1	0	1	**1**
Goksel *et al*. 1962 (36)	?	0	0	**0**	1	1	1	**1**
Karachaliou *et al*. 2005 (33)	Caucasian	Atypical abdominal	Atypical chest Atypical arthritis Response to colchicine (1.8 mg/d)	**1**	1	1	1	**1**
Ota *et al*. 1986 (19)	Japanese	Typical fever	Response to colchicine (1 mg/d)	**1**	0	0	1	**0**
Ocklitz *et al*. 1972 (37)	?	0	0	**0**	1	1	1	**1**
Ramadan *et al*. 1994 (39)	Mediterranean	Typical arthritis Atypical abdominal	0	**1**	0	0	1	**0**
Schwabe *et al*. 1988 (41)	Moroccan	Typical abdominal Typical arthritis	Atypical chest Response to colchicine (dose unknown)	**1**	1	1	1	**1**
Somers *et al*. 1957 (38)	?	0	0	**0**	1	1	1	**1**
Vilaseca *et al*. 1982 (42)	?	Typical arthritis	Response to colchicine (1 mg/d)	**1**	1	1	1	**1**

ence lists of selected articles and of several textbooks.

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

	Inflammation or clinical features of FMF	Effectiveness of Colchicine to prevent meningitis	Drug induced meningitis excluded	HSV-2 induced meningitis excluded	Cystic brain lesion excluded	Other systemic diseases excluded	Causality supported
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**

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, pecricarditis 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.iiii) 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.

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 sensibility 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 Behçet'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 systemic 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 meningits; 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 standardised 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.

References

1. YALCINKAYA F, OZCAKAR ZB, TANYILDIZ M, ELHAN AH: Familial Mediterranean fever in small children in Turkey. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S87-S90.
2. MASATLIOGLU S, DULUNDU E, GOGUS F, HATEMI G, OZDOGAN H: The frequency of familial Mediterranean fever in an emergency unit. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S44-S46.
3. OZTURK MA, KANBAY M, KASAPOGLU B *et al*.: Therapeutic approach to familial Mediterranean fever: a review update. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S77-S86. Erratum in: *Clin Exp Rheumatol* 2012; 30: 146.
4. FRENCH FMF CONSORTIUM: A candidate gene for familial Mediterranean fever. *Nat Genet* 1997; 17: 25-31.
5. THE INTERNATIONAL FMF CONSORTIUM: Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; 90: 797-807.
6. SHALABI M, WHITLEY RJ: Recurrent benign lymphocytic meningitis. *Clin Infect Dis* 2006; 43: 1194-7.
7. KALLIO-LAINE K, SEPPÄNEN M, KAUTIAINEN H *et al*.: Recurrent lymphocytic meningitis positive for Herpes simplex sirus type 2. *Emerg Infect Dis* 2009; 15: 1119-22.
8. JOLLES S, SEWELL WA, LEIGHTON C: Drug-induced aseptic meningitis: diagnosis and management. *Drug Saf* 2000; 22: 215-26.
9. ACHARD JM, LALLEMENT PY, VEYSSIER P: Recurrent aseptic meningitis secondary to intracranial epidermoid cyst and Mollaret's meningitis: two distinct entities or a single disease? A case report and a nosologic discussion. *Am J Med* 1990; 89: 807-10.
10. GINSBERG L, KIDD D: Chronic and recurrent meningitis. *Pract Neurol* 2008; 8: 348-61.
11. PRANDOTA J: Mollaret meningitis may be caused by reactivation of latent cerebral toxoplasmosis. *Int J Neurosci* 2009; 119: 1655-92.
12. VAZQUEZ F, BEGUELIN Y, SCHUTZ N, MAYORGA L: Collagen diseases and recurrent meningitis in an 88 year old patient. *Medicina* (B Aires) 2004; 64: 54-6.
13. GLEDHILL RF, LEWIS PD, MARSDEN CD, RAKE MO: Letter: Is Mollaret's meningitis another periodic disorder responsive to colchicine? *Lancet* 1975; 2: 415.
14. REIMANN HA: Mollaret meningitis. *JAMA* 1977; 237: 960-1.
15. REIMANN HA: Periodic disease; periodic fever, periodic abdominalgia, cyclic neutropenia, intermittent arthralgia, angioneurotic edema, anaphylactoid purpura and periodic paralysis. *JAMA* 1949; 141: 175-83.
16. FELD O, YAHALOM G, LIVNEH A: Neurologic and other systemic manifestations in FMF: published and own experience. *Best Pract Res Clin Rheumatol* 2012; 26: 119-33.
17. LIVNEH A, LANGEVITZ P, ZEMER D *et al*.: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40: 1879-85.
18. TEDDER DG, ASHLEY R, TYLER KL, LEVIN MJ: Herpes simplex virus infection as a cause of benign recurrent lymphocytic meningitis. *Ann Intern Med* 1994; 121: 334-8.

19. OTA K, SATO T, TAKAHASHI K: Periodic fever suppressed by colchicine - a case report. *Rinsho Shinkeigaku* 1986; 26: 792-6.
20. DELGADO JL, PORATH A, ARBELLE JE, HERISHANO Y: Familial Mediterranean fever (FMF) with aseptic meningitis and transverse myelitis: a case report. *First international conference on FMF*; Sept 7-11, 1997, Jerusalem, Israel.
21. FINSTERER J, STÖLLBERGER C, SHINAR Y: Cranial nerve lesions and abnormal visually evoked potentials associated with the M694V mutation in familial Mediterranean fever. *Clin Rheumatol* 2002; 21: 317-21.
22. KALYONCU U, EKER A, OGUZ KK *et al*.: Familial Mediterranean fever and central nervous system involvement: a case series. *Medicine* 2010; 89: 75-84.
23. KAPUR S, MUTAGI H, RAPHAEL J: Meningismus after metaraminol administration in a patient with Familial Mediterranean fever. *Can J Anaesth* 2006; 53: 1062-3.
24. MELENDRO JC: Letter: Mollaret's meningitis. *Lancet* 1975; 2: 932-3.
25. NAEYE RL: Cyclic fever, abdominal pain and grand mal seizures: case report. *Ann Intern Med* 1958; 48: 859-64.
26. NAJIM AL-DIN AS, MUBAIDIN A, WRIEKAT AL, ALQAM M: Risk factors of aseptic intracranial venous occlusive disease. *Acta Neurol Scand* 1994; 90: 412-6.
27. PRIEST RJ, NIXON RK: Familial recurring polyserositis: a disease entity. *Ann Intern Med* 1959; 51: 1253-74.
28. QUARTI-TREVANO GM, PAGANI M, POMA S *et al*.: False acute abdomen. *Minerva Chir* 1978; 33: 1325-38.
29. SCHILLER D, GRÖBNER S, BINDER L, MITTERMAYER H: A case of periodic fever. *Rev Med Interne* 2002; 23 (Suppl. 2): 247s-249s.
30. SIPAHIOGLU H: On paroxysmal polyserositis (Mediterranean fever) in our country, in connection with 5 cases, one of which presented signs of a periodic meningitis. *Turk Tip Cemiy Mecm* 1966; 32: 85-99.
31. TSALKIDIS A, GARDIKIS S, CASSIMOS D *et al*.: Acute abdomen in children due to extra-abdominal causes. *Pediatr Int* 2008; 50: 315-8.
32. WASHBURNE AC: Arizona medical problems consultation and case analysis. *Arizona Med* 1948; 5: 81-5.
33. KARACHALIOU I, KARACHALIOS G, CHARALABOPOULOS A, CHARALABOPOULOS K: Meningitis associated with familial Mediterranean fever. *Int J Clin Pract* 2005; 59 (Suppl. 147): S60-S61.
34. BARAKAT MH, MUSTAFA HT, SHAKIR RA: Mollaret's meningitis. A variant of recurrent hereditary polyserositis, both provoked by metaraminol. *Arch Neurol* 1988; 45: 926-7.
35. GEORGE RB, WESTFALL RE: Periodic meningitis: an unusual manifestation of periodic disease. *Ann Intern Med* 1965; 62: 778-85.
36. GOKSEL V, BOLUKOGLU MA, BANKMAN NH: Unusual syndromes and unpublished complications of periodic serositis (periodic disease). *Rev Med Moyen Orient* 1963; 20: 547-50.
37. OCKLITZ HW, HAHN M, PRENGEL M, SIEBERT H: Periodic syndrome with meningitis. *Dtsch Gesundheitsw* 1972; 27: 1272-8.
38. SOMERS K: Periodic disease: periodic fever; report of a case. *BMJ* 1957; 1: 1086-8.
39. RAMADAN N: Postmeningitic cluster headache. *Neurol* 1994; 44: 2208.
40. GEDALIA A, ZAMIR S: Neurologic manifestations in familial Mediterranean fever. *Pediatr Neurol* 1993; 9: 301-2.
41. SCHWABE A, MONROE J: Meningitis in familial Mediterranean fever. *Am J Med* 1988; 85: 715-7.
42. VILASECA J, TOR J, GUARDIA J, BACARDI R: Periodic meningitis and familial Mediterranean fever. *Arch Intern Med* 1982; 142: 378-9.
43. COLLARD M, SELLAL F, HIRSCH E, MUTSCHLER V, MARESCAUX C: Recurrent aseptic meningitis in periodic disease or Mollaret's meningitis? *Rev Neurol* 1991; 147: 403-5.
44. DEUTER CM, KÖTTER I, WALLACE GR, MURRAY PI, STÜBIGER N, ZIERHUT M: Behçet's disease: ocular effects and treatment. *Prog Retin Eye Res* 2008; 27: 111-36.
45. TAYLOR S, LIGHTMAN S: Recurrent anterior uveitis in patients with Vogt-Koyanagi-Harada syndrome. *Arch Ophthalmol* 2004; 122: 922-3.
46. D'CRUZ DP, KHAMASHTA MA, HUGHES GR: Systemic lupus erythematosus. *Lancet* 2007; 369: 587-96.
47. KASSAN SS, MOUTSOPOULOS HM: Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med* 2004; 164: 1275-84.
48. WARAKAULLE DR, ANSLOW P: Differential diagnosis of intracranial lesions with high signal on T1 or low signal on T2-weighted MRI. *Clin Radiol* 2003; 58: 922-33.
49. BARAKAT MH, EL-KHAWAD AO, GUMAA KA, EL-SOBKI NI, FENECH FF: Metaraminol provocative test: a specific diagnostic test for familial Mediterranean fever. *Lancet* 1984; 1: 56-7.
50. BEN-CHETRIT E, TOUITOU I: Familial Mediterranean fever in the world. *Arthritis Rheum* 2009; 61: 1447-53.
51. GLASZIOU P, CHALMERS I, RAWLINS M, MCCULLOCH P: When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007; 334: 349-51.
52. ARONSON JK, HAUBEN M: Anecdotes that provide definitive evidence. *BMJ* 2006; 333: 1267-9.
53. VANDENBROUCKE JP: In defense of case reports and case series. *Ann Intern Med* 2001; 134: 330-334.
54. STEICHEN O: Les rapports de cas, vestiges du passé? *Rev Mal Respir* 2007; 24: 271-4.