



Mediterranean spotted fever in the elderly: a prospective cohort study

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Abstract

The objective of this study is to evaluate the characteristics and outcome of elderly patients with Mediterranean spotted fever (MSF). This study was a prospective observational cohort study of all adult cases with confirmed MSF treated in a teaching hospital (1984–2015) to compare the characteristics of elderly patients (> 65 years) with younger adults. We identified 263 adult patients with MSF, and 53 (20.2%) were elderly. Severe MSF was more frequent in the elderly (26.4% vs. 10.5%; $p = 0.002$). Gastrointestinal symptoms, impaired consciousness, lung infiltrate, oedema, acute hearing loss, raised alanine transaminase, hyponatremia, and thrombocytopenia occurred more frequently in elderly patients, and arthromyalgia occurred less frequently. Most patients were treated with a single-day doxycycline regimen (two oral doses of 200 mg for 1 day). All patients recovered uneventfully. Fever disappeared 2.55 ± 1.16 days after treatment initiation in elderly patients, and the remaining symptoms disappeared after 3.65 ± 1.42 days. These figures were similar to non-elderly patients. Severe MSF was more frequent in elderly patients. Some clinical manifestations occurred with different frequencies in the elderly compared with younger patients. Single-day doxycycline therapy is an effective and well-tolerated treatment for MSF in elderly patients.

Keywords Mediterranean spotted fever · *Rickettsia conorii* · Elderly · Doxycycline · Tick-borne diseases · Severity

Introduction

Mediterranean spotted fever (MSF) is a tick-borne disease caused by *Rickettsia conorii* [1, 2]. MSF is endemic in the Mediterranean basin, but the incidence of MSF in Spain declined in recent decades [3, 4]. The annual incidence of MSF reported to the notifiable diseases surveillance system in Catalonia changed from 7.7 cases per 100,000 inhabitants in 1988 to 0.2 cases per 100,000 inhabitants in 2011, and it was accompanied by decreased seroprevalence in the human population [5]. MSF follows a benign course in most cases, but some cases present with a severe form that may lead to death

[6, 7]. MSF occurs in all age groups, but it develops most frequently in children and middle-aged adults [8]. Various studies demonstrated an association of severe forms of MSF with advanced age [1, 9]. However, no studies analysed the characteristics of MSF in elderly individuals.

The present study evaluated the clinical and epidemiological characteristics of MSF in elderly patients and compared these patients with non-elderly patients.

Materials and methods

Patients

All consecutive adult patients with MSF who presented between January 1984 and December 2015 to a 350-bed teaching hospital serving a population of approximately 200,000 were prospectively included in the study. Patients were classified into two age groups: > 65 years (elderly patients) and ≤ 65 years (non-elderly patients). The diagnostic criteria for MSF used were the presence of clinical manifestations compatible with MSF plus serological confirmation using indirect immunofluorescence assay for *R. conorii* (seroconversion

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from a negative titre to a titre of $\geq 1/80$ or a fourfold rise in titre between the acute and convalescent phases). All cases met the diagnostic criteria for MSF (score > 25) of the ESCAR (ESCMID Study Group on *Coxiella*, *Anaplasma*, *Rickettsia*, and *Bartonella*) [10].

Data collection and study definitions

All cases were directly evaluated by one of the authors (EE, MA, MM, or FB). Axillary temperature was taken every 6 h, and symptoms were evaluated daily until they disappeared. Apyrexia was defined as an axillary temperature < 37 °C. Information on underlying medical conditions was obtained via review of patients' medical records. Disease in all patients was controlled 30 days after onset to repeat the serological tests and evaluate the clinical outcome. Information on baseline and epidemiological characteristics, clinical features, laboratory values, antibiotic treatment, and outcome were prospectively collected in an anonymized database.

A case was considered to be severe if it met any of the following criteria: admission to an intensive care unit; presence of severe organ failure (heart, respiratory, central nervous system, renal, or hepatic failure); or the combination of three or more of the following characteristics: purpuric rash, hypotension (systolic blood pressure ≤ 90 mmHg), lung infiltrate, serum creatinine > 141 $\mu\text{mol/L}$, platelet count $< 100,000/\mu\text{L}$, rhabdomyolysis, serum albumin < 30 g/L, serum Na < 130 mEq/L, or proteinuria > 1 g/L, as previously described [8, 11].

Statistical analysis

Descriptive statistical analysis was performed using counts and percentages for categorical variables and means with standard deviation (SD) for continuous variables. Continuous variables were compared using the Student's *t* test or the Mann-Whitney *U* test, as appropriate. Categorical and stratified continuous variables were compared using the chi-square test or Fisher's exact test as appropriate. All analyses were performed using the SPSS software package v.15 (SPSS Inc., Chicago, IL, USA).

Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

Results

A total of 263 cases of MSF were identified in adult patients during the study period. Fifty-three cases (20.2%) were elderly (range 66–95 years), and 210 were non-elderly patients (range 18–65 years). Table 1 shows the epidemiological and clinical characteristics of the elderly and non-elderly patients.

The proportion of severe forms of MSF was significantly higher in the elderly patients, and severe forms were more frequent in elderly patients over 80 years (5/11; 45.5%) than elderly patients between 66 and 79 years (9/42; 21.4%), but this difference was not statistically significant ($p = 0.112$). Conversely, arthromyalgia was significantly less frequent in elderly patients and arthromyalgia was less frequent in elderly patients over 80 years (6/11; 54.5%) than elderly patients between 66 and 79 years (34/42; 81.0%; $p = 0.06$). Table 2 shows the main laboratory alterations. Thrombocytopenia, increased alanine transaminase, and hyponatremia were significantly more frequent in elderly patients.

Most patients (40 elderly and 143 non-elderly patients) received antibiotic treatment using a single-day doxycycline regimen (two oral doses of 200 mg, with an interval of 12 h, for 1 day) [11]. Some patients received other therapeutic regimens as part of several randomised clinical trials [12–15]. One elderly patient and two non-elderly patients did not receive antibiotic treatment because they presented to the hospital after symptoms of the disease had improved.

All patients recovered uneventfully, and no relapses were observed. Table 3 shows the clinical outcomes in elderly and non-elderly patients who received antibiotic treatment. Time to apyrexia and time to disappearance of the remaining symptoms (headache, arthromyalgia) were similar in both age groups. Fever disappeared earlier in elderly patients treated with the single-day doxycycline regimen than elderly patients treated with other antibiotics, but this difference did not reach statistical significance ($p = 0.058$). Likewise, fever disappeared somewhat later in severe cases (3.36 ± 1.80 days) than non-severe cases (2.71 ± 1.57 days), but this difference was not statistically significant ($p = 0.135$). The same pattern occurred in the interval until the disappearance of the remaining symptoms (4.36 ± 1.87 vs. 3.61 ± 1.42 days, $p = 0.127$).

Only one of the elderly patients treated with single-day doxycycline therapy experienced mild side effects of gastric discomfort, which may be related to the treatment.

Discussion

Adults over 65 years are the fastest growing population sector in industrialised and developing countries [16, 17]. Elderly people exhibit greater susceptibility to infections, which often occur with greater severity and atypical symptoms [18]. Therefore, there is growing interest in the study of the manifestations of infectious diseases in the elderly.

This report is the first study to describe the characteristics of MSF in elderly patients in detail. All of the cases met the diagnostic criteria for MSF [10] and were confirmed serologically.

The epidemiological, clinical, and biological characteristics of the patients included in this study were similar to those in other

Table 1 Epidemiological and clinical characteristics of elderly and non-elderly patients with MSF

Characteristics	Elderly <i>n</i> = 53 (%)	Non-elderly <i>n</i> = 210 (%)	<i>p</i> value
Sex (male)	28 (52.8)	138 (65.7)	0.082
Cases between June and September	50 (94.3)	192 (91.4)	0.584
Contact with dogs	42 (79.2)	182 (86.7)	0.174
Cases with comorbidities	34 ^a (64.2)	64 (30.5)	< 0.001
Severe MSF	14 (26.4)	22 (10.5)	0.002
Fever	53 (100)	210 (100)	NS*
Maculopapular rash	46 (86.8)	175 (83.3)	0.539
Purpuric rash	7 (13.2)	32 (15.2)	0.710
<i>Tache noire</i>	40 (75.5)	163 (77.6)	0.739
Headache	44 (83.0)	186 (88.6)	0.275
Arthromyalgia	40 (75.5)	184 (87.6)	0.026
Gastrointestinal symptoms ^b	21 (39.6)	51 (24.3)	0.025
Enlarged liver	17 (32.1)	68 (32.4)	0.966
Conjunctivitis	9 (17.0)	33 (15.7)	0.822
Impaired consciousness	8 (15.1)	11 (5.2)	0.013
Cough	6 (11.3)	25 (11.9)	0.906
Systolic arterial hypotension	5 (9.4)	13 (6.2)	0.373
Oedema	5 (9.4)	6 (2.9)	0.048
Vertigo	4 (7.5)	9 (4.3)	0.303
Acute hearing loss	4 (7.5)	2 (1.0)	0.016
Lung infiltrate	4 (7.5)	3 (1.4)	0.032
Hypoxemia	2 (3.8)	1 (0.5)	0.104
Other	5 ^c (9.4)	21 (10.0)	0.901

*NS not significant

^a Arterial hypertension (*n* = 10), diabetes (*n* = 7), chronic heart failure (*n* = 5), chronic alcoholism (*n* = 4), chronic bronchitis (*n* = 4), ischaemic heart disease (*n* = 3), Parkinson's disease (*n* = 1), hypothyroidism (*n* = 1), peripheral vascular disease (*n* = 1)

^b Nausea, vomiting, diarrhoea, or abdominal discomfort

^c Arthritis, phlebitis, acute heart failure, oculoglandular syndrome, or enlarged spleen (one case of each)

studies [2, 3, 8, 19, 20]. The higher proportion of women as elderly patients is likely due to their greater life expectancy [21]. An association of severe forms of MSF with advanced

age was observed in this study, and this association was described previously [7, 9, 11, 19]. This relationship is likely due to the impairment in innate and adaptive immunity, the reduced

Table 2 Primary laboratory abnormalities in elderly and non-elderly patients with MSF^a

Laboratory finding	Elderly <i>n</i> = 53 (%)	Non-elderly <i>n</i> = 210 (%)	<i>p</i> value
Haemoglobin < 12 g/dL	4/52 (7.7)	20/208 (9.6)	0.794
Leukocyte count > 10,000/μL	6/53 (11.3)	27/208 (13.0)	0.745
Leukocyte count < 5000/μL	8/53 (15.1)	47/208 (22.6)	0.231
Platelets < 150,000/μL	31/49 (63.3)	82/193 (42.5)	0.009
Aspartate transaminase > 40 IU/L	42/52 (80.8)	137/206 (66.5)	0.046
Alanine transaminase > 40 IU/L	33/52 (63.5)	122/202 (60.4)	0.686
Alkaline phosphatase > 130 IU/L	19/51 (37.3)	49/199 (24.6)	0.070
Creatinine > 130 μmol/L	5/50 (10.0)	11/201 (5.5)	0.240
Lactate dehydrogenase > 480 IU/L	14/47 (29.8)	53/173 (30.6)	0.910
Creatine phosphokinase > 200 IU/L	11/50 (22.0)	28/190 (14.7)	0.215
Na < 130 mEq/L	10/50 (20.0)	16/197 (8.1)	0.014
Albumin < 30 g/L	8/50 (16.0)	17/193 (8.8)	0.135

^a The denominator for each finding is variable because of missing data

Table 3 Clinical outcomes of elderly and non-elderly patients with MSF treated with antibiotics

Clinical response	Elderly	Non-elderly	<i>p</i> value
Patients treated with single-day doxycycline therapy ^a (<i>n</i>)	40	143	
Interval (days) between onset of symptoms and start of therapy (mean ± SD)	4.93 ± 2.73	4.75 ± 1.98	0.888
Interval (days) between start of therapy and disappearance of fever (mean ± SD)	2.55 ± 1.16	2.54 ± 1.17	0.992
Interval (days) between start of therapy and disappearance of symptoms ^b (mean ± SD)	3.65 ± 1.42	3.62 ± 1.34	0.771
Patients treated with other antibiotic regimens ^c (<i>n</i>)	12	65	
Interval (days) between onset of symptoms and start of therapy (mean ± SD)	4.17 ± 1.67	4.95 ± 1.99	0.183
Interval (days) between start of therapy and disappearance of fever (mean ± SD)	4.00 ± 2.42	3.25 ± 1.68	0.417
Interval (days) between start of therapy and disappearance of symptoms ^b (mean ± SD)	4.33 ± 1.97	4.03 ± 1.74	0.810

^a Two oral doses of 200 mg of doxycycline for 1 day

^b Headache, arthromyalgia

^c Tetracycline hydrochloride (10 days), josamycin (5 days), rifampin (5 days), or roxithromycin (5 days)

physiological reserve capacity, and the increased prevalence of chronic underlying diseases that occur in the elderly [18, 22–25].

The usual manifestations of MSF, such as fever, rash, black eschar (*tache noire*), and headache, occurred in the elderly as often as in non-elderly patients. Notably, the elderly patients presented arthromyalgia less frequently than the non-elderly patients. We do not have an explanation for this finding, but it may be related to the lower muscle mass in the elderly due to sarcopenia [26]. Gastrointestinal symptoms (nausea, vomiting, diarrhoea, or abdominal discomfort), impaired consciousness (stupor or confusion), lung infiltrate, oedema, and acute hearing loss occurred more frequently in elderly patients, likely due to the greater fragility of the organ systems [18]. The higher frequency of hyponatremia observed in elderly patients is not surprising because decreased serum sodium concentration is a rather frequent electrolyte disorder in the elderly population due to the presence of factors that contribute to increased antidiuretic hormone [27].

Antibiotic therapy administration during the first days of MSF shortens symptoms duration and helps prevent the progression to severe disease and associated mortality [28]. Doxycycline is the most active antibiotic against *R. conorii*, and it is the treatment of choice for MSF [1, 11, 28, 29]. Several studies demonstrated that single-day doxycycline therapy (two oral doses of 200 mg for 1 day) was an effective and well-tolerated treatment for MSF, including severe cases [11–15]. Most patients in the present study received this regimen, which has been the treatment of choice at our institution for MSF patients since 1990. The outcome was favourable in all patients, but the disappearance of fever and other symptoms occurred somewhat later in severe cases compared with non-severe cases. Notably, the times to reach apyrexia and the disappearance of symptoms were similar in the elderly and

younger patients, despite the significantly higher percentage of severe forms in the elderly. The treatment was very well tolerated by the elderly patients, and only one patient experienced mild adverse symptoms possibly related to the treatment.

The strengths of this study are its prospective design and the use of strict diagnostic criteria. The primary limitation of the study is that some factors that may influence disease severity or the response to treatment, such as the comorbidity index of Charlson or the previous functional state, were not considered. Another limitation is the performance of the study in a single centre. Therefore, we could not evaluate possible geographical differences in the virulence of *R. conorii*, which may produce different clinical manifestations or responses to treatment [1, 30]. Finally, it should be taken into account that, although *R. conorii* is the etiologic agent of MSF, other *Rickettsia* spp., such as *Rickettsia monacensis*, *Rickettsia sibirica mongolitimonae*, and *Rickettsia massiliae*, can occasionally cause an MSF-like illness [31]. Since serological cross-reactivity can occur between *R. conorii* and other *Rickettsia* spp., it cannot be ruled out that some cases in this study may be due to one of these *Rickettsia* spp.

In conclusion, elderly patients with MSF presented severe forms of the disease more frequently than non-elderly adults. Some clinical manifestations of MSF occurred with different frequencies in the elderly compared with non-elderly patients. Single-day doxycycline therapy is an effective and well-tolerated treatment for MSF in elderly patients.

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Author's contribution EE and FB were involved in the study design. EE, MA, MCG, MM, and AF were involved in data acquisition. All authors were involved in data analysis and interpretation.

EE and FB drafted the manuscript.

MA, MCG, JP, MM, and AF revised the manuscript critically for important intellectual content. All authors approved the final version to be submitted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Institutional Review Board. This study complied with the principles of the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was waived because no intervention was involved, and no identifying patient information was included.

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