



Severe clinical forms of Mediterranean spotted fever: a case series from an endemic area in Bulgaria

Teške kliničke forme mediteranske pegave groznice: serija slučajeva iz endemskog područja Bugarske

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Abstract

Background/Aim. Mediterranean spotted fever (MSF) belongs to Rickettsioses, the Spotted fever group (SFG). The causal agent is *Rickettsia conorii conorii* and the transmission to humans occurs through dog tick *Rhipicephalus sanguineus* bites. The aim of this study was to describe clinical and laboratory characteristics in patients with severe form of Mediterranean spotted fever admitted to Bulgarian university hospital in endemic region. **Methods.** A retrospective study was conducted at Stara Zagora University Hospital (Southeastern Bulgaria) between April 2015 and August 2016. During the analyzed period, 58 cases had clinical and laboratory data for MSF. Serological tests were applied for the etiological diagnosis. MSF-specific immunoglobulin (IgM) and IgG antibodies were detected in serum by indirect immunoenzyme assay (ELISA IgG/IgM, Viracell, Spain) – *R. conorii* ELISA IgG sensitivity 85%, specificity 100% and *R. conorii* ELISA IgM sensitivity 94%, specificity 95%. Statistical analysis was made by MS Excel 2007 and SPSS Statistics, version 19.0. **Results.** Eighteen patients presented as severe forms. The predominant gender of them were males (78%) and 22% were females. The me-

dian age of the analyzed group was 55 years (range: 14–78 years). Ten patients developed hepatic disorder while 4 had neurological signs. Laboratory data showed thrombocytopenia in 15 patients, mean value of platelet (PLT) count for the whole group was $108.6 \pm 53.8 \times 10^9/L$. Liver enzymes were elevated with mean value of aspartate aminotransferase (AST) 161.4 ± 90.1 IU/L and alanine aminotransferase (ALT) 163.9 ± 81.5 IU/L. Acute phase reactant as C-reactive protein (CRP) had mean value of 140.3 mg/L (range: 9–230 mg/L). Kidney function was impaired in some cases; the mean value of creatinine for the studied group was $134.7 \mu\text{mol/L}$ (range: 78–313 $\mu\text{mol/L}$) and mean value of urea was 9.6 mmol/L (range: 4.2–27.4 mmol/L). **Conclusion.** Bulgaria is an endemic area for tick-borne diseases. Cases of MSF are reported annually. Severe forms of MSF are not rare. Typical clinical and laboratory markers for severity should be actively searched for. Early diagnosis and proper treatment is the key to avoid complications and enable patient recovery.

Key words: rickettsia; boutonneuse fever; ticks; bulgaria; serology; blood chemical analyses; diagnosis.

Apstrakt

Uvod/Cilj. Mediteranska pegava groznica (MPG) pripada riketiozama (grupl pegave groznice) – izaziva je *Rickettsia (R.) conorii conorii*, a prenosi se na ljude ujedom krpelja pasa *Rhipicephalus sanguineus*. Cilj ove studije bio je da se opišu kliničke i laboratorijske karakteristike bolesnika sa teškom formom MPG koji su bili hospitalizovani u univerzitetskoj bolnici u endemskom području Bugarske. **Metode.** Retrospektivna studija sprovedena je u Univerzitetskoj bolnici Stara Zagora (južnoistočna Bugarska) u periodu od aprila 2015. godi-

ne do avgusta 2016. godine. Tokom analiziranog perioda 58 bolesnika imalo je kliničke i laboratorijske znake MPG. Za potvrdu etiološke dijagnoze primenjeni su serološki testovi. Za MPG specifična imunoglobulinska (IG) antitela za IgM i IgG pronađena su u serumu imunoenzimskim indirektnim esejom (ELISA IgG/IgM, Viracell, Španija). *R. conorii* ELISA IgG senzitivnost bila je 85%, specifičnost 100%, a *R. conorii* ELISA IgM senzitivnost bila je 94%, specifičnost 95%. Statistička analiza urađena je u programu MS Excel 2007 i SPSS verzija 19.0. **Rezultati.** Osamnaest bolesnika imalo je težak oblik MPG. Muškarci (78%) su bili brojniji u odnosu na

žene (22%). Srednja vrednost starosti kod 18 analiziranih bolesnika bila je 55 godina (14–78 godina). Kod 10 bolesnika pojavili su se poremećaji funkcije jetre, a kod četiri, neurološki simptomi. U laboratorijskim analizama trombocitopenija se javila kod 15 bolesnika, a srednja vrednost trombocita u celoj grupi iznosila je $108,6 \pm 53,8 \times 10^9/L$. Jetreni enzimi bili su povišeni, a srednja vrednost aspartat aminotransferaze (AST) iznosila je $161,4 \pm 90,1 IU/L$, a alanin aminotransferaze (ALT) $163,9 \pm 81,5 IU/L$. Srednja vrednost reaktanata akutne faze kao što je C-reaktivni protein (CRP) iznosila je $140,3 mg/L$ (9–230 mg/L). Kod nekih bolesnika javio se poremećaj bubrežne funkcije. Srednja

vrednost kreatinina u posmatranoj grupi iznosila je $134,7 \mu mol/L$ (78–313 $\mu mol/L$), a ureje iznosila je $9,6 mmol/L$ (4,2–27,4). **Zaključak.** Bugarska je endemsko područje za bolesti nastale zbog ujeda krpelja. Slučajevi MPG se analiziraju na godišnjem nivou. Teški oblici MPG nisu retki. Tipične kliničke i laboratorijske markere za procenu težine bolesti treba aktivno pratiti. Rana dijagnoza i odgovarajuće lečenje ključni su za izbegavanje komplikacija i oporavak bolesnika.

Ključne reči: rickettsia; groznica, boutonneuse; krpelji; bugarska; serologija; krv, hemijske analize; dijagnoza.

Introduction

Mediterranean spotted fever (MSF) belongs to Rickettsioses, the Spotted fever group (SFG). The agent is *Rickettsia conorii conorii* and transmission to humans occurs through dog tick *Rhipicephalus sanguineus* bites. The disease is also called “Boutonneuse fever”, “Marseilles fever”, etc. and depends on the geographic region of its appearance¹. Historically, the illness was described for the first time in Tunisia in 1909 by Conor and Bruch². In 1923, the typical cutaneous lesion at the place of tick bite (tache noire) was drawn by Pieri in Marseilles³. The disease is endemic for Mediterranean region and northern Africa, although cases are reported in the central and eastern Europe, India, and southern Africa^{1,4}. Most of the Balkan countries (Bulgaria, Croatia, Greece, Romania, Serbia, Turkey) have reported the infection or serological data for the circulation^{4–10}. In Bulgaria, the infection was identified for the first time in 1948 by Vapzarov¹¹. For the period from 1948 to 1959 human cases are reported annually¹¹. After 1960, the incidence of cases dramatically decline because of the good veterinarian control of homeless dogs, rabies prophylaxis and improved agricultural measures¹². From 1993 to 2003, a new phase of re-emerging of the disease started, following a phase of declines for the period of 2004 to 2011¹¹. Since then (2011), some cases have been annually reported in the endemic area of Bulgaria^{5, 13–16}. These territories are located around the Maritsa riverside settlements and Black Sea. Few Bulgarian researchers reported their results for MSF.

The aim of this study was to describe clinical, epidemiological and laboratory characteristics in patients with severe forms of MSF who were admitted to Bulgarian University Hospital in the endemic region.

Methods

A retrospective study was conducted between April 2015 and August 2016 at the Department of Infectious Diseases, Stara Zagora University Hospital (Southeastern Bulgaria). Patients over 14 years with clinical, epidemiological and laboratory data for MSF were enrolled. Patients' records, historical and physical features, laboratory parameters, imaging investigations [radiography, abdominal ultrasound,

computed tomography (CT)] and invasive procedure (lumbar puncture) were collected and analyzed. Diagnostic criteria by Raoult et al.¹⁷, were applied and patients with diagnostic score more than 25 were analyzed further.

For severity, a complex criteria were enclosed. Severe forms are defined as presence of at least two laboratory criteria and at least one clinical criterion. Clinical symptoms were fever above 39°C, headache, nausea/vomiting, muscle/joint pain, abundant hemorrhagic rash (acute onset of intense skin rash with hemorrhagic characteristics with reddish to bluish-purple spots), clinical manifestation of one organ damage, elderly patients. Laboratory parameters were: white blood cells more than $12 \times 10^9/L$ or less than $5 \times 10^9/L$; platelet count $< 120 \times 10^9/L$; hemoglobin level below 110g/L; elevation of liver enzymes; creatinine and urea above the normal range.

The patients whose clinical and laboratory features fulfilled the criteria for severe forms continue the evaluation. Their symptoms, clinical findings, epidemiological data and laboratory features were analyzed.

Etiological diagnosis was made by serology tests. MSF-specific IgM and IgG antibodies were detected in serum by indirect immunoenzyme assay (ELISA IgG/IgM, Vircell, Spain) – *Rickettsia conorii* ELISA IgG sensitivity 85%, specificity 100% and *Rickettsia conorii* ELISA IgM sensitivity 94%, specificity 95%. Serum samples were collected at the day of admission and fourteen days later. The presence of antibodies of class IgM and following appearance of antibodies of class IgG were accepted for serological confirmation of clinical, epidemiological and laboratory data.

The medical procedures of this study were approved by the Local Ethics Committee of Stara Zagora University Hospital, Bulgaria (2 Stoletov Str., 6000 Stara Zagora)

Statistical analysis was made by MS Excel 2007 and SPSS Statistics, version 19.0. Average values (mean \pm SD) and a range were calculated for the laboratory parameters.

Results

For the period of one and a half year, 58 persons with MSF were hospitalized at Stara Zagora University Hospital (Southeastern Bulgaria, endemic area for MSF). Thirty-one percentages fulfilled the criteria of severe course and were

further analyzed. Males (77.8%) prevailed. The mean age was 54.9 ± 16.4 years. Underlying diseases were marked in 7 patients – all had hypertension except one who had diabetes mellitus type 2. The median of hospital stay was 7.5 days. Sixteen patients developed the illness during the typical season for the occurrence (May–October). All analyzed cases were residents from the endemic area of *R. conorii conorii*. Contacts with dogs (direct or dog care) were mentioned in 61.1% of the cases, but 9 noted tick bites. The patients developed typical clinical presentation (fever, rash, flu-like symptoms) and they mentioned epidemiological risk factors, but the severity of the illness was an indispensable reason for the hospital admission (Figures 1 and 2). Main clinical signs are presented in Table 1. Mean value of fever height was $39.2^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and headache was mentioned in 50% of the cases. Craniopharyngeal syndrome (a presentation of red face, redness of conjunctiva, hyperemia of neck and upper thorax to clavicle) was marked in 7 cases. Gastrointestinal signs were presented in 33.3%, central neural system disorders were noted in 22.2%, pulmonary involvement was found in 16.7% and kidney failure in 27.8% of cases. In contrast to these manifestations, hepatic injury was estimated in 77.8% of the cases.



Fig. 1 – Rash in a 47-year-old man with Mediterranean spotted fever (MSF).



Fig. 2 – Rash in a 45-year-old patient infected by *Rickettsia conorii conorii*.

Laboratory findings are presented in Table 2. The median value of hemoglobin was 130.5g/L (range: 99 g/L–165 g/L), white blood cells had the median of $7.4 \times 10^9/\text{L}$ (range: $1.4 \times 10^9/\text{L}$ – $16 \times 10^9/\text{L}$), the median value of platelet count was $106 \times 10^9/\text{L}$ (range: $37 \times 10^9/\text{L}$ – $226 \times 10^9/\text{L}$). The mean value of fibrinogen was 3.7 ± 0.8 g/L, erythrocyte sedimentation rate (ESR) had mean value of 27.2 ± 20.8 mm/h and the mean value of CRP was 140.3 ± 69.8 mg/L. Liver enzymes were elevated in almost all cases with the median value of AST 154.4 U/L (range: 36 U/L–356.7 U/L) and 174.0 U/L of ALT (range: 36 U/L–299 U/L). Kidney parameters demonstrated deviations: the mean values of creatinine was 134.7 ± 73.1 $\mu\text{mol/L}$ and 9.6 ± 6.7 mmol/L of urea. Cerebrospinal fluid (CSF) abnormalities were estimated in 3 examined cases.

Serological tests confirmed the disease. Specific antibodies of class IgM were detected from the first serum samples and two weeks later, antibodies of class IgG were found.

A complex therapy was applied. Fluoroquinolones were administered as a first choice; it was recommended to take 400 mg of Ciprofloxacin intravenously twice a day over 7–10 days in all patients. Seven patients were treated with a combination therapy doxycycline (100 mg twice a day) and ciprofloxacin (400 mg twice a day) for 10 days. Ceftriaxone (2.0 g once a day intravenously) was added empirically to the therapy in cases with pneumonia. Supportive therapy as

infusions, hepatoprotective drugs, corticosteroids and antipyretic medications were used. All patients recovered after a complex treatment. There were no complications and consequences in the follow-up period.

Table 1

Epidemiological and clinical data of patients with severe Mediterranean spotted fever (MSF)

Patient (N)	Gender/Age	Month of admission	Tick bites	Eschar	Hemorrhagic rash	Muscle/Joint pain	Hepatomegaly/Splenomegaly
1	M/60	August	Yes	No	No	Yes	Yes/No
2	M/59	June	No	Yes	Yes	Yes	Yes/No
3	F/45	May	Yes	No	No	No	Yes/No
4	M/64	July	Yes	Yes	Yes	Yes	Yes/Yes
5	M/32	June	No	Yes	Yes	Yes	Yes/No
6	M/51	May	No	No	No	Yes	No/No
7	M/60	August	Yes	No	No	Yes	No/Yes
8	M/14	August	No	No	No	Yes	Yes/No
9	M/78	August	Yes	No	No	Yes	No/No
10	M/51	April	Yes	Yes	No	No	Yes/No
11	F/75	July	No	No	No	Yes	No/No
12	F/70	July	No	No	No	Yes	Yes/No
13	M/47	July	No	No	No	Yes	Yes/No
14	M/77	May	No	No	Yes	Yes	Yes/Yes
15	M/47	April	Yes	Yes	Yes	Yes	Yes/Yes
16	M/45	October	No	Yes	No	Yes	Yes/No
17	M/67	May	Yes	Yes	No	Yes	Yes/No
18	F/47	July	Yes	Yes	No	Yes	Yes/No

M – male; F – female.

Table 2

Laboratory data of 18 patients with severe Mediterranean spotted fever (MSF)

Patient	WBC (3.5–10.5 ×10 ⁹ /L)	PLT (150–400 ×10 ⁹ /L)	PT (70–110%)	CRP (0.0–5.0 mg/L)	AST/ALT (5–40 IU/L)	Creatinine (58–110 μmol/L)	Urea (2.8–8.3 mmol/L)	Diagnosis
1	10.6	96	46	217	162/240	85	6.4	MSF & Hepatic Involvement
2	10.5	226	76	ND	103/97	99	7.6	MSF & Hepatic Involvement
3	6.7	138	69	210	253.9/220.6	78	9.3	MSF & Hepatic Involvement
4	11.7	119	98	123	140/165	141	21.36	MSF & Meningoencephalitis
5	3.6	64	97	138.5	165/231	99	5.4	MSF & Hepatic Involvement
6	5.2	168	89	43.2	50/44	91	4.5	MSF & Pneumonia
7	16	168		ND	36/51	111	7.6	MSF & Pneumonia
8	2.8	56	84.3	230	50/36	90	6	MSF
9	13.9	62	104.2	ND	167.8/89.3	105	7.9	MSF & Neurological Disorder
10	4.4	51	85.1	ND	222.5/155.3	303	13.5	MSF & Hepatic Involvement
11	8.1	135	83.3	187	147/183	313	27.4	MSF & Hepatic Involvement
12	9	82	89	135.6	98.9/86.5	211	20.1	MSF & Encephalitis
13	6.2	93	96.1	ND	193.2/209.5	103	5.2	MSF & Hepatic Involvement
14	1.4	42	113.2	9	290/247.5	105	4.3	MSF & Hepatic Involvement
15	10.8	37	124	136.4	356.7/299	203.6	8.5	MSF & Hepatic Involvement
16	6.4	116	92.4	ND	74/134	101	7.1	MSF & Pneumonia
17	6.4	184	80	ND	123.3/265	85	6.4	MSF & Hepatic Involvement
18	11.6	117	85	113.4	272/196	101	4.2	MSF & Meningoencephalitis

Note: WBC – White blood cells; PLT – Platelet count; PT – Prothrombin time; CRP – C-reactive protein; AST – aspartate transaminase; ALT – alanine transaminase; ND – no data available.

Discussion

The present study described clinical, epidemiological and laboratory data in 18 cases with MSF presented as severe clinical forms. The aim of the analysis was to exclude mild and moderate forms and to characterize the specific features in cases with severe disease course. The estimate of 31% of severe forms for the presented period was a high percentage when compared to other publications^{8, 13, 18, 19}. One of the explanations is the limitation of the study. Patients with signs of complications or other disorders were directly hospitalized. Probably many cases with mild and moderate forms were treated as outpatients and they were not included in our analysis.

The mean age of 54.9 years is similar to other reports^{4, 8, 20}. Males were the predominant gender in our study. Reports from France¹⁸, Greece²⁰ and Romania⁴ also estimated high proportion of male gender. In contrast, Kuloglu et al.⁸ found slight prevalence of females. The sex ratio is influenced by local characteristics regarding agricultural work, livestock farming and housekeeping. The seasonal occurrence for MSF in our study is the typical for the rickettsioses^{10, 20–22}. Most of our patients had contacts with dogs and 50% of them mentioned tick bites which were predispositions for developing a tick-borne disease. Similar epidemiological data were identified by Pitigoi et al.⁴, Romdhane et al.²³ and Kuloglu et al.²⁴. The clinical symptoms and signs were similar to ones presented in other studies^{4, 8, 13, 15, 20, 23–26}. The leading clinical features in severe forms were high fever with severe headache, hepatomegaly/splenomegaly and the combination of older age and underlying diseases. Similar symptoms are reported by Raoult et al.¹⁹ and Kuloglu et al.⁸. The accompanying diseases according to our data were hypertension and *diabetes mellitus* which did not differ from others studies^{8, 21, 24}. Neurological disturbances and pulmonary disorders were described by other authors as leading clinical findings in severe and malignant forms^{8, 20, 27, 28}. Laboratory data from the presented study established liver impairment, kidney failure, marked elevation of CRP, alteration in CSF and thrombopenia. Those laboratory findings were not distinguished by other studies in Europe^{4, 8, 19, 20, 25, 27, 28}. Severe case with neurological deterioration, renal impairment, thrombocytopenia and enlarged liver enzymes was reported by Tzavella et al.²⁸. Aliaga et al.²⁷ presented an old diabetic man with encephalitis, thrombocytopenia and acute renal failure. Our neurological cases characterized with similar symptoms and disorders. In our study, no neurological sequences were detected as in Greek²⁸ and Turkish reports⁸. In contrast, Spanish report described developing of severe sequelae²⁷. Pulmonary infiltrates were demonstrated in 27% of a Greek study²⁰, one patient had pneumonia in other report⁸, 43% of severe cases of pneumonitis was displayed in a French investigation¹⁹. In comparison, 3 of our patients

developed pneumonia. Gastrointestinal signs were not rare in the presented study. Yilmaz et al.²⁵ observed gastrointestinal complaints in 25% and Raoult et al.¹⁹ noted diarrhea in 14% of severe cases. Acute renal failure was mentioned as a risk factor for fatal outcome¹⁶. Kidney disorders at different levels were found in 5 of our patients, but with no lethal outcome. Renal dysfunction was revealed in the case of severe MSF with encephalitis. The man survived with neurological complications²⁷. In our study, timely and appropriate treatment was applied. Therefore, no deaths or subsequent complications occurred in the follow-up period.

The region of Stara Zagora (Southeastern Bulgaria) is an endemic area for tick-borne diseases and close attention to rickettsioses was paid. In summer time, every suspected case with fever and rash is carefully examined and those suspected of severe forms of infectious diseases are directly guided to an infectious diseases specialist. Because of that procedure, there is a high percentage of hospitalized cases with severe forms of MSF and with favorable outcome. The clinical signs does not differ from those in other reports. Severe cases are characterized by typical laboratory disturbances and predominant liver and kidney involvement, CSF manifestation and pulmonary and gastrointestinal symptoms. The discrete differences between the reports are due to the local characteristics, national habits, investigations features, time and place of study.

Conclusion

The MSF is still endemic disease in Bulgaria and a trend towards an increase of severe cases is real. The surveillance of this disease should be continuous with an emphasis on severe cases and risk factors. In any case with fever, rash and epidemiological data for vector-borne disease, MSF should be suspected. An appropriate treatment should be provided for positive outcome.

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Conflicts of interest

None of the authors have any associations that might be deemed a conflict of interest to the publication of this manuscript. Parts of this manuscript are coming to be presented at 6th International Meeting on Emerging Diseases and Surveillance (IMED 2016), 04–07 November 2016, Vienna, Austria (Abstract #0610 – Poster session).

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